Assessment of head and neck lymphoedema: The importance of the patient perspective

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

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Abstract

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Title: Assessment of head and neck lymphoedema: The importance of the patient perspective

Background: Head and neck lymphoedema (HNL) is an important contributor to function and quality of life (QoL) following head and neck cancer (HNC) treatment. Despite this, there are limitations to the currently available tools to assess HNL, including a lack of instruments to measure the impact of HNL on a patient's QoL.

Aims: The primary aims of this dissertation are to identify and explore currently available tools for assessment of HNL and to develop a patient reported QoL instrument specific to HNL, grounded in the patient perspective.

Methods: A systematic review of tools used in the assessment of HNL was completed and published (Chapter 3). Initial development of an HNL QoL tool included qualitative interviews of patients with HNL. Interviews were transcribed and analysed using inductive thematic analysis (Chapter 6). Data from these qualitative interviews were then used to generate initial items for the QoL instrument. These items were rated for clarity, importance, and intrusiveness by patients with HNL as well as expert clinicians using a Qualtrics survey. Based on these results, the pilot instrument was refined, and proceeded to further validation via three-step cognitive interviews with patients with HNL. The pilot instrument, titled the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN) was further refined based on these interviews and prepared for future validation and psychometric efforts (Chapter 7).

Results: The results of the systematic review confirmed that there is no available QoL instrument designed specifically for individuals with HNL. Qualitative interviews conducted with 22 individuals with HNL revealed issues around identity, lifestyle, discomfort, and vulnerability. Commonly cited concerns were the basis for item generation, which resulted in 130 initial items, reduced to 73 through a binning and winnowing process. These items were assessed by 9 clinicians and 9 patients with HNL and ranked according to importance and clarity. Based on this feedback, 52 items were preserved. Five participants completed three-step cognitive interviews and based on their feedback; 33 items were retained for the pilot version of the CALI-HaN. Of the items retained, there was 1 global, 10 physical, 7 functional, and 15 emotional items.

Conclusions: The focus of this thesis was on exploring the patient experience with HNL to develop a patient reported QoL instrument. We identified physical, functional, and emotional consequences of HNL which were integrated into the development of the CALI-HaN. The extensive focus on the patient perspective during development contributes to strong content validity. Future psychometric testing of the CALI-HaN will follow completion of the PhD.

Acknowledgements

I would like to express my most sincere gratitude to my doctoral committee, Professors Joanne Patterson, Gemma Cherry, Jason Fleming, and Bridget Young for their support, encouragement, insight, and humanity. There were many challenges that arose over the period of study that none of us anticipated. Your grace in supporting me through this process was heart-warming and I will always carry a deep appreciation for all you have done for me. I have benefitted so much from your expertise and guidance.

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This thesis would also not be possible without the input of patients who were gracious enough to share their experience and expertise in living with head and neck lymphoedema. It is only through your voices that we can learn how to do better as providers. Thank you so much for your willingness to share so candidly.

Dedication

Every successful researcher must have a strong foundation upon which to stand. I dedicate this thesis to my home team for their unwavering support, encouragement, and love throughout this entire process. To my loving husband, William Starmer, I'm not sure you really knew what you were getting into when you married me. Thanks for staying the course with me and always encouraging me to reach for my dreams. To my incredible offspring, Max Starmer, Caitlin Starmer, and Alyssa Starmer – you inspire me. Thank you for helping me to be better in everything I do. I hope I do you proud like you do me proud! To my parents, Gail Brokaw and Michael Brokaw, thank you for providing me with all the science experiments I wanted growing up and for helping me believe anything was possible. To my siblings, Julia Francis, Cyrus Vattes, and Daniel Merchalle – thank you for pushing me to be the best I could be. I love you all.

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Abbreviations

ABSSD:	American Board of Swallowing and Swallowing Disorders
AHNS:	American Head and Neck Society
ASCO:	American Society of Clinical Oncology
ASHA:	American Speech Language Hearing Association
BIS:	Bioimpedance spectroscopy
CDT:	Complete decongestive therapy
COS:	Core outcome set
COSMIN:	Consensus-based Standards for the selection of health Measurement Instruments
DIGEST-FEES:	Dynamic Imaging Grade of Swallowing Toxicity – FEES
DRS:	Dysphagia Research Society
EORTC:	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-H&N 43	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire: Head & Neck 43
ePROM	Electronic Patient Reported Outcome Measures
ESMO	European Society for Medical Oncology
FACT-HN	Functional Assessment of Cancer Therapy-Head and Neck
FEES:	Flexible endoscopic evaluation of swallowing
FOIS:	Functional Oral Intake Scale
GT:	Grounded Theory
HNC:	Head and neck cancer
HNCA:	Head and Neck Cancer Alliance
HNL:	Head and neck lymphoedema
HPV:	Human papilloma virus
HRQoL:	Health-related quality of life
ICG:	Indocyanine green
IMPT:	Intensity modulated proton therapy
IMRT:	Intensity modulated radiation therapy
IPA:	Interpretive Phenomenological Analysis
MIC:	Minimally important change
MRI:	Magnetic resonance imaging
NCI	National Cancer Institute
PBDA:	Pattern-based Discourse Analysis
PICO:	Participants, Interventions, Comparisons, Outcomes
PROM:	Patient reported outcome measure
QoL:	Quality of life
QUADAS:	Quality Assessment of Diagnostic Accuracy Studies
ROS:	Reactive Oxygen Species
SRQR:	Standards for Reporting Qualitative Research

TA:	Thematic Analysis
TBD:	To be determined
TLM:	Transoral Laser Microsurgery
TORS:	Transoral Robotic Surgery
UK:	United Kingdom
US:	United States
VAS:	Visual Analogue Scale
VHNSS:	Vanderbilt Head and Neck Symptom Survey
WHO:	World Health Organization

Project timeline

TASK	0-6 months	6-12 months	12-18 months	18-24 months	Year 3	Year 4
Systematic review and manuscript preparation	X	X				
Ethics applications	X	X				
Qualitative interviews			X			
Analysis of qualitative data and manuscript preparation				X		
Preparation of Qualtrics survey				X		
Analysis of Qualtrics data and instrument development				X		
Three step interviews and instrument refinement					X	
Patient-reported outcome measure development manuscript preparation					X	
Thesis writing						X

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1. Introduction to thesis

1.1. Rationale for thesis

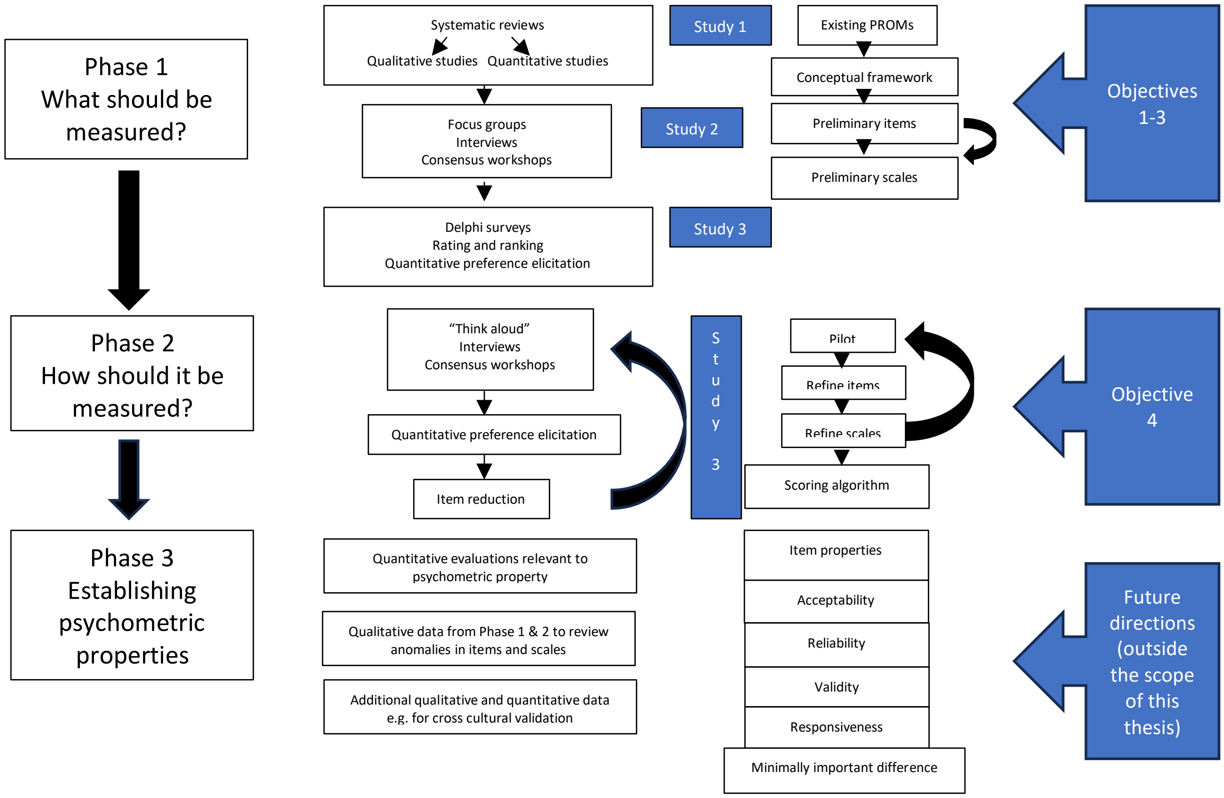
Lymphoedema is a condition that arises when the lymphatic system is unable to process lymphatic fluid in an efficient and effective manner, leading to stagnation of lymph fluid in the interstitial space. Head and neck lymphoedema (HNL) is a common condition experienced by the majority of individuals treated for head and neck cancer (HNC), with incidence rates as high as 90% (Deng, Murphy et al., 2013; Jackson et al., 2016, Ridner et al., 2016). Lymphoedema can result in acute and chronic issues impacting physical function and comfort, functional participation in meaningful life activities, and socioemotional well-being. Whilst it is increasingly recognised that HNL plays an important role in quality of life (QoL) following HNC treatment (Deng, Murphy, et al., 2013), there is a lack of agreement regarding how to best assess and measure this condition. Without valid and reliable assessment tools, it is impossible to study the efficacy and patient-perceived impact of lymphoedema therapies in this population. Whilst there are a small number of tools used to measure the physical aspects and severity of HNL, there are no extant tools available to measure the impact of HNL on QoL, particularly the psychosocial contributions to QoL. Thus, there is a need for development of a patient-focused measure of QoL related to HNL.

1.2. Aims and objectives of thesis

As a clinician providing care to patients with HNL, I have felt inadequately prepared to identify and measure the multi-faceted impacts of HNL on QoL. There is not a tool in my clinical armamentarium that allows me to gauge the relative impact of HNL on an individual patient, nor the impact on patient well-being of the treatments I provide. Thus, the primary aim of this thesis is to explore the state of the science regarding HNL assessment and to initiate the development of a patient-reported outcome measure (PROM) to be used in this population. Whilst there are a variety of issues that may result in HNL (e.g. burns), the focus of this thesis will be on HNL related to HNC. A particular emphasis of this work is the concentrated exploration of the patient experience living with HNL to establish a meaningful patient-reported outcome tool. The patient voice and experience are central to this thesis.

Howell et al. (2022) provided a framework for the development of patient-centric outcome measures, including determining what should be measured, how it should be measured, and establishing the psychometric properties of the measure (Figure 1-1). The intent of this thesis was to focus on Phase 1 (what should be measured) and Phase 2 (how it should be measured) with an emphasis on deeply exploring the patient perspective. In addition to the patient perspective, it was also important to include clinician perspectives about *what* should be measured regarding HNL QoL and *how* it should be measured. This focus on patient and clinician perspectives was designed to contribute to strong content validity of the tool under development.

Figure 1-1 Thesis mapped to Howell's development process for patient-reported outcome measures (Howell et al., 2022)



As highlighted in Figure 1-1, this thesis has four primary objectives.

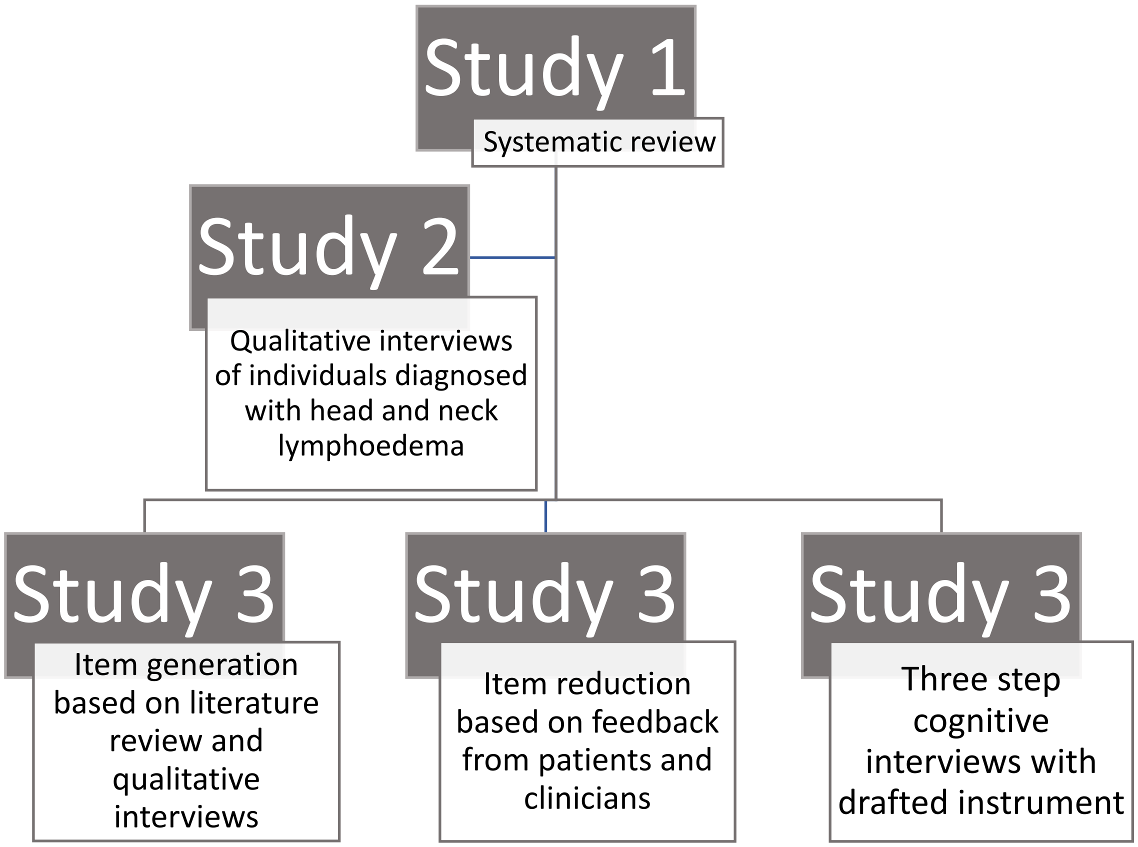
1. Identify the measures currently used in the assessment and measurement of head and neck lymphoedema and assess their validity and reliability. This was achieved through a systematic review using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) framework (Mokkink et al., 2018) (Study 1). This systematic review identified a lack of a patient reported QoL instrument specific to HNC patients with HNL. This shortcoming became the impetus for objectives 2-4.

2. Identify key themes expressed by patients with HNL regarding how it has impacted their lives. This aim was based on recommendations for developing QoL instruments that are grounded in the patient perspective. This aim was accomplished through completion of a series of semi-structured qualitative interviews of individuals identified as having HNL (Study 2).
3. Develop a set of candidate questions based on qualitative interviews to be used as the foundation of a patient-reported HNL-specific QoL instrument. Candidate questions were initially generated from the semi-structured interviews described above. Further item bank refinement was based on feedback from key stakeholders including patients with HNL and clinical providers with expertise in HNC and lymphoedema via online surveys and interviews (Study 3).
4. Refine the patient-reported HNL-specific QoL measure for further field testing and validation. This included qualitative three-step cognitive interviews regarding the draft instrument with individuals living with HNL (Study 3).

1.3. Overview of the studies

This thesis uses a multiple methods approach and incorporates both qualitative and quantitative methods. This combination of quantitative and qualitative methods is necessary to achieve the overarching goal of this work: to identify shortcomings in HNL assessment and provide solutions that will be of value for clinicians, researchers, and the patients we serve. The studies presented here share this same principal goal. Study one (Chapter 3) outlines a systematic review of the literature conducted to identify the current state of the science in HNL assessment. Study two (Chapter 6) is a qualitative study designed to elicit the lived experiences of those with HNL to better represent those experiences during the development of a patient reported QoL instrument. Study three (Chapter 7) describes the quantitative and qualitative methods employed in the initial development of the pilot instrument, the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN). Figure 1-2 provides a schematic of these three studies.

Figure 1-2 Schematic representation of thesis studies



1.4. Thesis structure

This thesis is offered in an alternative format with embedding peer-reviewed publications representing the three studies conducted. Each of these chapters has been submitted for publication in a peer-reviewed journal and at the time of thesis completion each manuscript has been accepted for publication. I am the first author for each publication. As first author, I conceptualised, planned, and executed each of these studies with input from included co-authors. This included study inception, design, and development; data collection, analysis, and interpretation; and manuscript preparation, submission, and revision. Co-authors participated in study design, data interpretation, subject recruitment, manuscript review, and supervisory oversight. I prepared the remainder of this thesis with supervisory feedback.

This thesis is comprised of eight chapters. Chapter 1 provides the rationale for and the structure of this submitted thesis. Chapter 2 provides a review of the pertinent background literature with a focus on introductory information about HNC and its treatments, treatment toxicity related to HNC treatment, the normal and abnormal lymphatic system, head and neck lymphoedema, and strategies employed historically for measuring lymphoedema. Chapter 3 provides an overview of recommended methodology for completion of systematic reviews and concludes with the first published manuscript describing a systematic review conducted to elucidate the state of the science in HNL assessment (Study 1). This systematic review was performed to identify what tools have been used in the measurement of HNL to establish areas of opportunity for development. Based upon the identified lack of tools to measure the impact of HNL on QoL, Study 2 was designed to elicit patient perspectives of factors impacting on HNL related QoL. Chapter 4 provides insight into the theory of health-related quality-of-life and how it is measured. It also includes background on qualitative research methods used to ascertain patients' perspectives of factors impacting QoL. Chapter 5 reviews the science and methodology of PROM development. Chapter 6 is the second published manuscript which presents data from a series of qualitative interviews of individuals with HNL. Chapter 7 is the third published manuscript describing the methods employed in the initial development of an HNL-specific QoL instrument, the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN). Finally, Chapter 8 provides a summary and discussion of the work here presented as well as future directions for this research following completion of this thesis.

Study 1 was accepted in the journal, *Lymphatic Research and Biology,* impact factor 1.4.

> Starmer, H.M., Cherry, M.G., Patterson, J., Young, B., Fleming, J. (2023). Assessment of measures of head and neck lymphedema following head and neck cancer treatment: A systematic review. *Lymphatic Research and Biology*. 21(1): 42-51.
>
> https://doi.org/10.1089/lrb.2021.0100

Study 2 was accepted in the journal, *Supportive Care in Cancer,* impact factor 3.5.

Starmer, H.M., Patterson, J., Fleming, J., Cherry, M.G., Young, B. (2023). Head and neck lymphedema and quality of life: The patient perspective. *Supportive Care in Cancer*. 31(12): 696.

https://doi.org/10.1007/s00520-23-08150-2

Study 3 was accepted in the journal, *Head and Neck,* impact factor 3.82.

Starmer, H.M., Patterson, J., Young, B., Fleming, J., Cherry, M.G. (2024). Development of an head and neck lymphoedema specific quality of life tool: The Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN). *Head and Neck,* epub ahead of print. https://doi.org/10.1002/hed.27704

1.5. Rationale for thesis submission in the alternative format

This thesis is submitted in the alternative format to ensure the timely dissemination of research findings. As there is a growing interest in the study of HNL globally, the timely presentation of these research findings allows other researchers the opportunity to benefit from this work without unnecessary duplication of efforts, and to ensure access to the most updated information.

1.6. About the Author

I am a speech-language therapist in the United States with 24 years' experience providing rehabilitative services to individuals with HNC. I completed my bachelor's degree in Communicative Disorders at California State University – Long Beach in 1998 and my master's degree in Communication Sciences and Disorders at the University of Pittsburgh in 2000. The first six years of my career I focused on building my clinical skills and developed a keen interest in HNC whilst working at the Veteran's Administration hospital in Pittsburgh, PA.

In 2006 I began my first academic position at Johns Hopkins University within the Department of Otolaryngology – Head and Neck Surgery. During my time at Johns Hopkins, I was the co-founder of the Multidisciplinary Head and Neck Cancer Clinic where newly diagnosed patients with HNC had the opportunity to meet with surgical, medical, and radiation oncologists as well as a speech-language therapist to discuss treatment recommendations. To support my interest in conducting clinical research, I completed the Johns Hopkins Certificate Program in Clinical Investigation in 2011. My research whilst at Johns Hopkins was multidisciplinary in nature and focused predominantly on function and outcomes related to HNC. I had particular interest in developing strategies to enhance adherence to rehabilitative interventions during HNC treatment. Innovative work included establishing the use of prophylactic gabapentin during head and neck radiation to minimise mucositis associated pain (Starmer et al., 2014; Starmer et al., 2017; Yang et al., 2016) as well as development of a mobile app to support patients in completing their exercises during head and neck radiation (Starmer et al., 2018). I rose from the position of Clinical Instructor to Assistant Professor during my nine years at Johns Hopkins.

In 2014 I was recruited to Stanford University to establish and build the Head and Neck Speech and Swallowing Rehabilitation Program. Since the inception of the program, it has grown to employ 4 full-time speech and language therapists providing outpatient care to individuals with HNC. I founded the head and neck lymphoedema (HNL) program in 2018. I continued with research endeavors initiated whilst I was at Johns Hopkins including leading a multi-centre clinical trial of our mobile app, HNC Virtual Coach (Starmer et al., 2023) and collaborated with international colleagues in the development of the Dynamic Imaging Grade of Swallowing Toxicity for FEES (DIGEST-FEES) (Starmer et al., 2021) and the refinement of the Patterson Oedema Scale (Starmer et al., 2021). Additionally, with the clinical development of lymphoedema services, my research interests have grown to include HNL assessment and treatment. I was promoted to Clinical Associate Professor in 2018 and to Clinical Professor in 2023. I have published more than 70 peer-reviewed papers, written 16 text-book chapters, and presented over 200 presentations nationally and internationally. In 2023, I was awarded the prestigious American Speech Language Hearing Association (ASHA) Fellow designation in recognition for my clinical, research, and instructional contributions in HNC rehabilitation. I currently serve on the board of the Head and Neck Cancer Alliance (HNCA), as co-chair of the American Head and Neck Society (AHNS) Survivorship, Supportive Care, & Rehabilitation service, as co-chair of the Continuing Education committee of the American Board of Swallowing and Swallowing Disorders (ABSSD), and co-chair of the Membership committee of the Dysphagia Research Society (DRS).

Since founding the HNL program at Stanford, I have been keenly interested in studying clinical outcomes specific to HNL. My first publication looking at different models of HNL care brought to my attention some of the limitations of available tools to measure HNL (Yao et al., 2020). I had some concerns regarding the reliability of tape measures. Additionally, I lamented that there was no other method to capture change in response to treatment, such as changes in socioemotional status. These observations, alongside my dissatisfaction with available PROMs to capture the impact of HNL led me to pursue the current research. As a clinician-researcher, I am enthusiastic and hopeful that this contribution will benefit patients, clinicians, and researchers for many years to come.

2. Background literature

2.1. Chapter overview

It is important to understand the context in which HNL-related QoL exists. Thus, this chapter aims to provide the reader with important background information including information about HNC and its treatments, the pathophysiology and impact of lymphoedema, lymphoedema specific to the head and neck region, and traditional methods used to assess lymphoedema. This chapter is meant to serve as a review of the most salient information relevant to this thesis, rather than a comprehensive systematic review of all topics.

2.2. Head and neck cancer

HNC is the sixth most common cancer globally and includes cancers arising from the oral cavity, oropharynx, nasopharynx, larynx, hypopharynx, nasal passages, salivary glands, and the thyroid gland. Historically, exposure to toxins such as tobacco and alcohol was implicated as the primary cause of most HNC in the developed world (Haugen et al., 2023). In recent years, with substantial public health emphasis on smoking cessation in many developed nations, there has been a decrease in the incidence of HNC related to tobacco exposure (Rettig & D’souza, 2015). At the same time, there has been an increase in awareness of the role of viruses as an important aetiology of HNC.

2.2.1. Virally associated head and neck cancer

The Human Papillomavirus (HPV) and the Epstein Barr Virus (EBV) have been increasingly implicated as causative aetiologies of oropharyngeal and nasopharyngeal cancers respectively (Gillison et al., 2015; Kamran et al., 2015). Virally associated HNCs are more frequently seen in younger patients and have more favorable oncologic outcomes than non-virally associated HNC (Chen et al., 2019; Lechner et al., 2022; Zhu et al., 2022). Despite this survival advantage, patients with virally associated HNC may experience greater decrements to their QoL (Sharma et al., 2012). Additionally, due to a higher likelihood of being active in the work force due to younger age at diagnosis, these individuals may have a greater impact on their economic stability – further impacting their QoL (Granstrom et al., 2020; Lenze et al., 2022; Lu et al., 2019). Finally, earlier age at diagnosis and favorable survival rates may result in a longer period when the side effects of treatment may impact an individual treated for virally related HNC, thus increasing the overall QoL burden (Bigelow et al., 2020; McDowell et al., 2021). Thus, in recent years there has been an increased focus on researching issues relevant to function and QoL in patients with HNC, with an emphasis on prevention of issues known to negatively impact QoL such as swallowing impairment, communication issues, and lymphoedema.

2.2.2. Head and neck cancer treatments

Treatment of HNC often involves surgery, radiation, and/or systemic agents like chemotherapy and immunotherapy, all of which may have functional repercussions (Table 2-1). Minimally invasive surgical options such as Transoral Robotic Surgery

(TORS) and Transoral Laser Microsurgery (TLM) have emerged as less toxic options compared to traditional open surgical approaches, however, are only appropriate for select cases (Hardman et al., 2020; Nagel, Chang, & Hinni, 2022). Advances in radiation-based therapies such as Intensity-Modulated Radiation Therapy (IMRT) and Intensity Modulated Proton Therapy (IMPT) have been developed with the primary goal of reducing treatment toxicities such as xerostomia and dysphagia (Alterio et al., 2019; Moreno et al., 2019). Similarly, systemic therapies such as those that block epidermal growth factor receptors (EGFR) have emerged as potential alternatives to traditional chemotherapies to minimise treatment toxicities such as hearing loss and peripheral neuropathy (Gold et al., 2009). Recently, there has been great interest in the potential role of immunotherapy in the management of HNC, though the impact of these therapies on function are not well understood currently (Vallianou et al., 2023).

Table 2-1 Examples of treatment modalities used in the treatment of head and neck cancer

Surgery	**Radiation therapy**	**Systemic therapy**
Primary tumour resection • TORS • TLM • Open surgical resection	Photon-based radiation • Intensity modulated radiation therapy (IMRT) • 3-Dimensional conformal radiation therapy (3D-CRT)	Chemotherapy • Cisplatin • Carboplatin • Paclitaxel
Lymph node dissection	Proton-based radiation	Targeted therapies • Cetuximab
Reconstruction		Immunotherapies • Nivolumab

Despite the interest in developing less toxic treatments for this disease, all the currently prevalent treatments may have lasting functional repercussions. Surgical resection often alters critical anatomy in the upper aerodigestive tract. This may result in functional issues impacting speech, swallowing, and breathing function. In addition, surgical resection may result in injury to nerves such as the vagal and hypoglossal nerves that are involved with both sensory and motor functions. The impact of scar and other soft tissue changes may further complicate functional recovery through diminished mobility. Removal or disruption of lymphatic structures may result in lymphoedema which will be discussed at greater length in section 2.5.

Whilst non-surgical approaches such as radiotherapy maintain the structural integrity of the upper aerodigestive system, radiation damage to the soft tissue, circulatory system, lymphatic system, and cranial nerves may also result in functional impairments. Functional impairments following head and neck radiation include xerostomia, dysgeusia, and dysphagia, among others (List & Bilir, 2004). Post-treatment toxicities may impact body image, social and vocational participation, cognition, communication, and nutrition (Ringash et al., 2018). Multimodal therapy including a combination of two or all three treatment modalities is common in patients with advanced stage HNC (Lango, 2009), and both acute and chronic treatment-related toxicities increase with the application of multimodality treatment (Fahy et al., 2023, Machtay et al., 2008).

2.2.3. Quality of life in head and neck cancer

QoL is increasingly understood to be a very important consideration in the treatment of HNC. Historically, poor cure rates necessitated application of aggressive anti-cancer therapies regardless of the impact they had on function and quality of life. Fortunately, with improved cure rates, particularly in those with virally associated HNC, there has been more opportunity to try to limit treatment toxicity. With the publication of “From Cancer Patient to Cancer Survivor: Lost in Transition,” (Hewett et al., 2006) a substantial focus on patient reported outcomes and QoL arose, particularly within HNC research. Whilst global measures of QoL often return to pre-treatment baseline levels one year following HNC treatment, a number of long-term symptoms may persist and impact long-term QoL (Klein et al., 2014; Semple et al., 2008; So et al., 2012). Poorer QoL has been associated with advanced stage tumours, extensive surgeries including those requiring free-flap reconstruction, neck dissection, combined chemoradiotherapy, post-operative radiotherapy, feeding tube or tracheostomy dependence, and co-morbidities (Klein et al., 2014; Murphy, Gilbert, & Ridner, 2007; Rathod et al., 2015). Unmet needs in HNC survivorship are common, impacting more than 50% of patients, with a detrimental impact on QoL (Giulani et al., 2016; Ringash et al., 2018). It is critical to understand the primary drivers of QoL impairment to develop and apply interventions that may positively impact QoL.

2.2.4. Dysphagia after head and neck cancer treatment

Swallowing impairment, or dysphagia is widely understood to be a primary driver of QoL following HNC treatment (Høxbroe Michaelsen et al., 2017; Maurer et al., 2011;

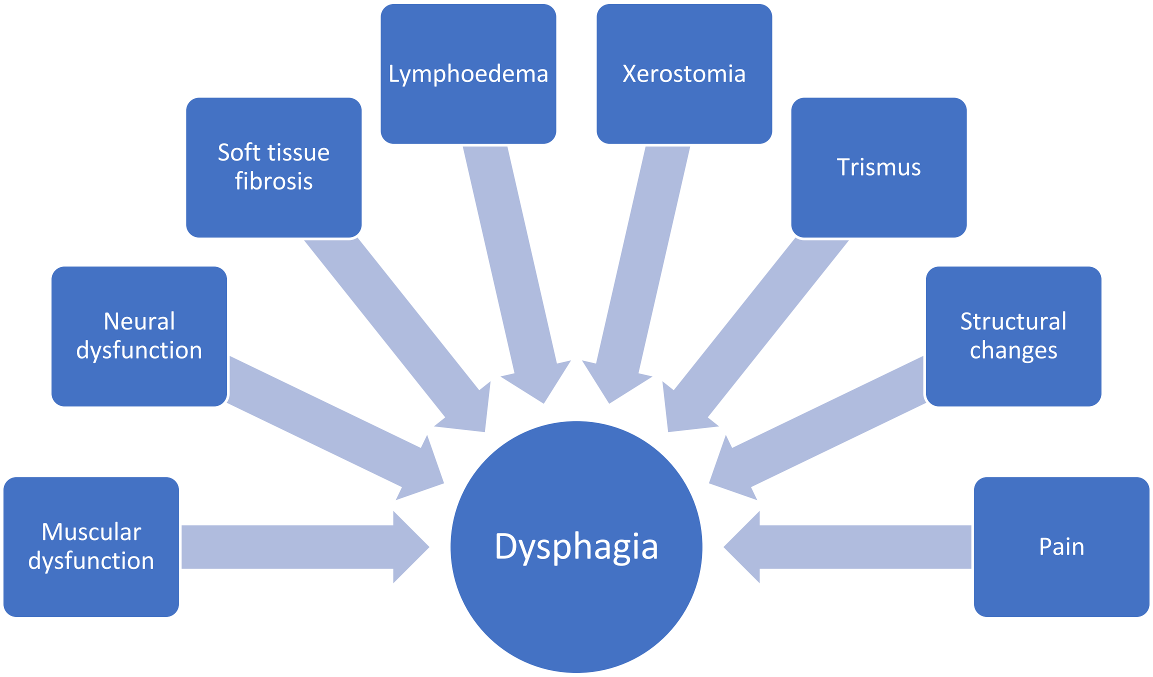
Nguyen et al., 2005; So et al., 2012). Because of the social nature of eating and drinking in most societies, the inability to participate in these important social connections can be distressing to patients and lead to isolation (Dornan et al., 2022; Pezdirec et al., 2019). Fear and anxiety around choking are commonly reported by patients with dysphagia and are under-reported by clinicians and caregivers (Ekberg et al., 2002; Martino et al., 2010; Nguyen et al., 2005; Nund et al., 2014). As a result, oropharyngeal dysphagia after HNC treatment is associated with a greater risk of depression and distress (Krebbers et al., 2023; Lin et al., 2012). In addition to the substantial impact of post HNC dysphagia on QoL and psychosocial well-being, post-treatment dysphagia may be associated with increased risk of mortality due to aspiration pneumonia (Forastiere et al., 2013; Mortensen et al., 2013; Xu et al., 2015). As such, it is of paramount importance that HNC care teams consider ways to prevent and treat dysphagia to mitigate these long-term impacts.

2.2.5. Contributing factors to post head and neck cancer dysphagia

There are several chronic toxicities of HNC treatment that may impact swallowing function and swallowing related QoL (Figure 2-1). Xerostomia, or dry mouth, is a common concern of patients who have received head and neck radiation, with prevalence rates around 50% for moderate-severe xerostomia (Little et al., 2012; Nutting et al., 2011). Patients with chronic xerostomia report inadequate saliva, thickened saliva texture, and changes in food and drink consumed due to salivary changes (Messmer et al., 2011). Trismus, or restricted mouth opening can also increase difficulty with eating following treatment for HNC, with prevalence rates ranging from 5-38% (Dijkstra et al., 2004).

Whilst xerostomia and trismus may impact eating function, neuromuscular dysfunction is a primary pathophysiology of dysphagia in patients following HNC treatment. Such dysfunction may occur because of surgical alterations to muscles and nerves associated with swallowing, radiation induced changes in these structures, and/or changes in sensation (King et al., 2016; Murphy & Gilbert, 2009). Fibrosis and atrophy are two primary contributors to post-radiation dysphagia and are likely related to the extent of acute inflammation during treatment (King et al., 2016; Murphy & Gilbert, 2009). This acute inflammation can be contrasted with lymphoedema (discussed below) which is a more chronic form of oedema related to damage to the lymphatic structures. Radiation therapy creates a nearly immediate inflammatory response in the treated tissues which then leads to a cascade of events including excessive fibrin production which may lead to fibrosclerosis (King et al., 2016; Stubblefield, 2011). This fibrosis has been implicated in nerve dysfunction, neuropathic pain, and focal neuropathies – all of which may impact swallowing function (Karri et al., 2021; King et al., 2016; Stubblefield, 2011). Atrophy refers to reduced bulk and force generating capacity of muscles which can be related to disuse during HNC treatment, underlying structural changes in the muscle from the radiation treatment, or denervation (Benedict et al., 2023). Whilst many individuals will see improvement or resolution of acute effects of treatment 3-6 months after treatment is concluded, in a subset of patients, chronic or late effects may be seen (Murphy & Gilbert, 2009). Because dysphagia is a large driver of post-treatment QoL and has been implicated as a cause of non-cancer mortality post-treatment, there is great interest in elucidating the underlying pathophysiology of post-HNC treatment dysphagia to develop efficacious preventative and rehabilitative models of care.

Figure 2-1 Contributing factors to development of dysphagia after HNC treatment



2.2.6. Lymphoedema and dysphagia in head and neck cancer

Another treatment related toxicity, lymphoedema may be seen in up to 90% of HNC survivors (Deng et al., 2012; Jackson et al., 2016, Ridner et al., 2016). Lymphoedema can be seen in external structures such as the face and neck or in internal structures such as the pharynx and larynx. There is an increasing appreciation of the relationship between lymphoedema and dysphagia in patients following HNC treatment (Jeans et al., 2022; Queilia et al., 2020; Starmer Hutcheson, & Patterson, 2023). For example, patients with more severe internal HNL are more likely to have impairment of pharyngeal clearing forces and airway protection (Jeans et al., 2022; Starmer, Hutcheson, & Patterson, 2023). Understanding the relationship between HNL and dysphagia is a necessary foundation to establishing interventions to target lymphoedema in order to mitigate post-HNC swallowing dysfunction and associated impairment in QoL.

2.3. The lymphatic system

The lymphatic system is part of the immune system and is responsible for the transport of interstitial fluid and waste products from diverse regions of the body to the venous system for reabsorption and disposal. The lymphatic system is comprised of lymphatic organs, lymphatic vessels, and pre-lymphatic channels. Red bone marrow and the thymus gland are considered primary lymphatic organs whilst the lymph nodes, spleen, and mucosal epithelial tissue are considered secondary lymph organs. Lymphocytes originate in the bone marrow and mature in the secondary lymph organs as they are exposed to a variety of antigens. Their primary role is to mount an immune response to foreign antigens.

Lymph capillaries are the most distal aspect of the lymphatic system and are responsible for the absorption of excess fluids in the interstitial spaces. These thin-walled vessels transport fluids to the lymph vessels which transport fluids to and from the lymph nodes through afferent and efferent channels. Lymph vessels contain one-way valves that ensure unidirectional flow of lymph fluid to prevent backflow. The afferent lymph vessels transport fluid to the lymph nodes and the efferent lymph vessels carry fluid away from the lymph nodes to the venous system. Fluid transport through the lymph vessels is influenced by fluid load, the circulatory system, and muscle contraction. Increased heart rate and muscle contraction tend to facilitate transport whilst excessive fluid load tends to inhibit transport.

The lymph nodes are distributed throughout the body and serve to filter lymphatic fluid, mount immune responses to foreign antigens, and trap pathogens to minimise collateral damage and cancer metastasis (Janhardan et al., 2023). The head and neck region is particularly densely populated with lymph nodes and vessels (Pan et al., 2008). Because of their role in filtering malignant cells, lymph nodes are commonly targeted in patients with advanced stage cancer through either surgical removal or directed radiation therapy. Both the removal and radiation of lymphatic structures may impair lymphatic drainage, leading to lymphoedema. A recent publication of a rat model of lymphoedema demonstrated that rats undergoing lymphadenectomy followed by irradiation had slower lymphatic drainage, increased oedema and subcutaneous thickness, inflammation, and fibrosis than those undergoing a sham operation (Daneshgaran et al., 2019).

2.4. Lymphatic dysfunction

Lymphoedema has been defined as “a localized form of tissue swelling caused by excessive retention of lymphatic fluid in the interstitial compartment” (Grada & Phillips, 2017, p.1009). When the lymphatic load exceeds the transport capacity of the lymphatic system, or when there is mechanical insufficiency of the lymphatic system, lymphoedema may occur. The result is chronic stasis of protein-rich fluid which presents as inflammation and can result in development of fibrosis if untreated.

Lymphoedema can be described as either a primary (congenital) condition or a secondary condition, frequently resulting from cancer-related care. Secondary lymphoedema is more common than primary lymphoedema and is estimated to impact up to 200 million individuals globally (Grada & Phillips, 2017). A systematic review and meta-analysis by Cormier et al. (2010) found a 15.5% incidence of secondary lymphoedema for those treated for a variety of cancers, with receipt of radiation therapy increasing risk to 31%.

2.5. Head and neck lymphoedema

The head and neck region is replete with lymph nodes and lymphatic vessels which makes it particularly vulnerable to lymphatic injury (Lee et al., 2018). In HNC, lymphoedema may be related to obstruction of the lymphatic channels due to the physical impacts of tumours, scar, or fibrosis; or may be related to removal or injury of lymph nodes and vessels during surgical resection or radiation therapy (McGarvey et al., 2013). As a result, there may be accumulation of protein-rich lymphatic fluid in the interstitial space of the head and neck region. The accumulation of this fluid in turn stimulates an ongoing inflammatory response and connective tissue deposition. This cascade of events can then lead to progressive fibrosis which can further impair lymphatic function (Deng et al., 2010).

2.5.1. Functional impairment associated with head and neck lymphoedema

HNL is an increasingly recognised contributor to post HNC functional impairment and has been documented to occur in up to 90% of HNC survivors (Deng, Ridner, et al., 2012; Jackson et al., 2016; Ridner et al., 2016). This oedema may result in compressive symptoms, reduced mobility of impacted structures, inflammation, and fibrosis, all of which may contribute to dysphagia and other functional impairments (Deng, Murphy, et al., 2013; Murphy & Ridner, 2010; Ridner et al., 2016). More severe HNL has been associated with poorer patient reported swallowing outcomes (Deng, Murphy, et al., 2013; Jackson et al., 2016). Lymphoedema may be seen externally in the neck, face, and submental area, but also internally in structures of the oral cavity, pharynx, and larynx (Deng, Ridner, et al., 2012; Lewin et al., 2010). Examples of internal and external oedema can be referenced in figures 2-2 through 2-5.

Figure 2-2 Internal oedema of the epiglottis (starred) visualised during endoscopic examination

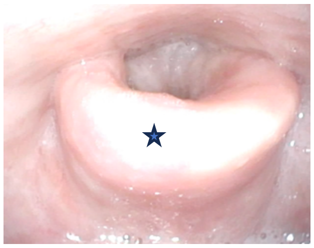


Figure 2-3 Internal oedema of the aryepiglottic folds (A) and arytenoids (B) visualised during endoscopic examination

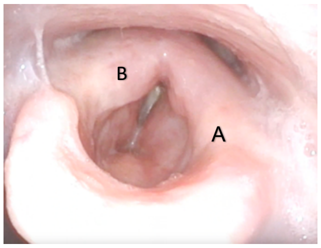


Figure 2-4 Internal oedema of the arytenoids (A) and posterior pharyngeal wall (B) visualised during video fluoroscopy

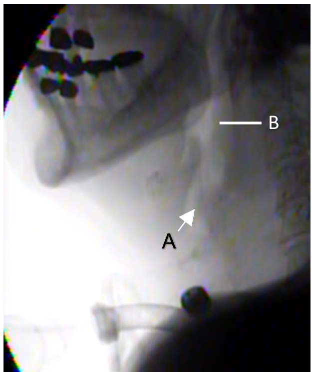
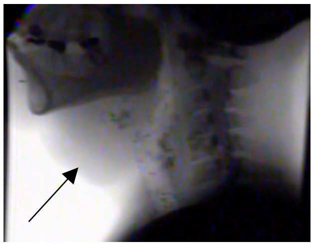


Figure 2-5 External oedema of the submandibular region visualised during video fluoroscopy



2.5.2. Head and neck lymphoedema development

Post-treatment oedema is common following surgery and radiation, and generally resolves without treatment by 3 months (Deng, Ridner, et al., 2013). When oedema persists beyond 3 months, it is considered lymphoedema. HNL arises when the lymphatic system is unable to keep up with lymphatic load, thus allowing lymph to remain stagnant in the interstitial spaces of the head and neck region (Murphy et al., 2007). This accumulation of lymph fluid and the associated chronic inflammation may lead to fibrosclerotic changes if left untreated (Deng et al., 2013; Ridner et al., 2016). Evidence has shown that development of lymphoedema is most common in the 3-6 months immediately following treatment with development of fibrosis occurring approximately three months later (Ridner et al., 2016). It is important, however, to acknowledge that the methods used to establish the trajectory of lymphoedema and fibrosis development in this study may have influenced the results. Patients were assessed at baseline, 3-6 months, 9 months, and 12 months post treatment, therefore there may be an artificial categorization of these timelines. Additional information regarding the natural history of lymphoedema in the head and neck is needed.

Early during the development of external lymphoedema, there may not be visible evidence of oedema, however the patient may report a sense of fullness or tightness in the impacted region (Smith & Lewin, 2010). As the lymphoedema progresses, soft oedema is commonly noted in the submental region, but also may occur in the face or neck. Generally, lymphoedema at this stage is reversable in response to treatment (Smith et al., 2014). If left untreated, this oedema may progress to a point of pitting oedema (Deng, Murphy, et al., 2013; Ridner et al., 2016). Pitting oedema is indicative of more advanced stage lymphoedema and may progress to development of fibrosis. Whilst evidence is needed regarding timing of lymphoedema treatment, it appears to be key to identify lymphoedema early and to provide treatments that minimise the potential of oedema advancing to fibrosis which is believed to be the primary factor influencing long-term swallowing function (King et al., 2016).

2.5.3. Internal lymphoedema

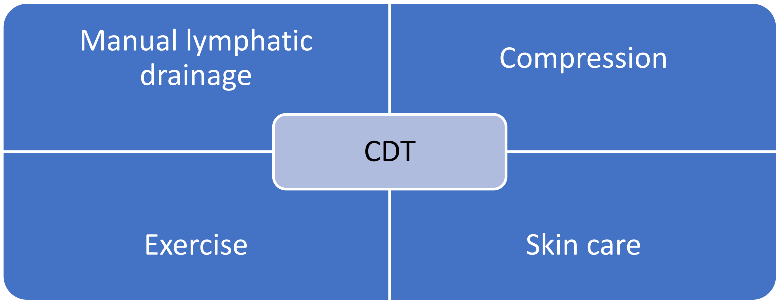
Internal lymphoedema poses a particular challenge for early identification, as patients are not generally able to self-identify it. Though patients routinely undergo endoscopic visualisation of the larynx and pharynx for disease surveillance, it is uncommon for physicians to identify oedema unless it is severe enough to threaten the airway. Prevalence rates of internal oedema vary widely, largely due to inconsistent reporting metrics for internal lymphoedema, however there is evidence that internal lymphoedema may be more prevalent than external lymphoedema (Deng et al., 2012; Jeans et al., 2020). The (Revised) Patterson Oedema Scale (Patterson et al., 2007; Starmer et al., 2021) provides a framework for the rating of internal lymphoedema and has been increasingly adopted by HNC clinicians globally. It has been reported that the structures most likely to be involved with internal lymphoedema include the epiglottis, arytenoids, and aryepiglottic folds (Jeans et al., 2020; Starmer, Hutcheson, & Patterson, 2023), structures that are critically involved in the swallowing process, and particularly with airway protection. A recent study demonstrated that oedema of the epiglottis, vallecula, pharyngoepiglottic folds, pyriform sinuses and false vocal folds were associated with impaired swallowing efficiency (i.e. pharyngeal residue), whilst edema of the false vocal folds and pyriform sinuses were associated with impaired swallowing safety (i.e. laryngeal penetration/aspiration) (Starmer, Hutcheson, & Patterson, 2023). Given the emerging evidence of the relationship between internal oedema and dysphagia, it is important to consider the presence of such oedema in patients with post HNC dysphagia.

2.5.4. Head and neck lymphoedema treatment

The treatment of lymphoedema commonly involves several interventions known collectively as "complete decongestive therapy" or CDT (Figure 2-6). This treatment includes manual lymphatic drainage (MLD), compression, skin care, and regional exercises (Lewin et al., 2010). The goal of CDT is to stimulate lymphatic flow, redirect the collected fluid towards a functional drainage system, and to prevent the fluid from re-accumulating. Limited evidence demonstrates improvement in HNL in response to CDT treatment (Piso et al., 2001; Smith et al., 2015). Mullan et al. (2023) published a synthesis of current literature regarding lymphoedema therapy. Based on the heterogeneity in the literature, they were unable to determine the relative benefit of different intervention approaches, which included MLD, compression, kinesiotaping, and pneumatic compression, among others. In the twelve studies that met inclusion criteria, they found substantial variability in management of HNL and advocated for personalised treatment plans that include adherence optimisation considerations due to poor adherence rates across trials. A major limitation to available interventional studies for HNL is related to a lack of consensus regarding which tools to use (Mullan et al., 2023).

Additionally, there is a lack of validation of measures by which changes may be quantified (Arends et al., 2023; Deng, Ridner, Aulino, & Murphy, 2015; Starmer, Cherry, et al., 2023). Most studies have focused on the treatment and assessment of external HNL and no studies to date have specifically addressed techniques to address internal HNL.

Figure 2-6 Components of Complete Decongestive Therapy



2.6. Traditional methods for lymphoedema measurement

The diagnosis of lymphoedema is typically based upon a clinical exam which takes into consideration patient symptoms, physical examination, and medical history. Lymphoedema has been measured and categorised in several ways. The most common general staging system for lymphoedema severity in all sites was developed by the International Society of Lymphedema (2020) (Table 2-2).

Table 2-2 International Society of Lymphedema Severity Staging System

Lymphoedema stage	Description
Stage 0	Subclinical oedema – injury present but no visible swelling
Stage 1	Visible oedema that responds to elevation
Stage 2	Presence of pitting oedema
Stage 3	Progression to fibrosis and adipose deposition

Patients with Stage 0 lymphoedema will often complain of a sense of pressure or heaviness in the impacted region. Stage 1 lymphoedema is generally seen in the acute phase of lymphoedema development when oedema becomes visually apparent. Stage 2 lymphoedema may arise as the condition progresses, often with pitting, which does not respond to elevation. Pitting refers to an indentation that remains after pressure is applied to a region of swelling and typically indicates a high burden of fluid content in the interstitial spaces. Stage 3 lymphedema is characterised by firm tissue and lack of pitting and is irreversible. In addition to categorising the severity of oedema, several volumetric, imaging, and psychosocial/patient-reported outcome measures have been described.

2.6.1. Volumetric measures of lymphoedema

Volumetric measures include water displacement and circumferential tape measures. Water displacement measures include the submersion of the oedematous structure into a cylinder of water and determining what percentage of water volume was displaced. Historically, a 10% difference in displacement of water compared to the contralateral limb was used as the criteria for diagnosing limb lymphoedema (DiSipio et al., 2013). In recent years, this method has been utilised less frequently due to issues around imprecision, difficulty replicating results, and contraindications in those with skin conditions (Deltombe et al., 2007). Furthermore, this method is not appropriate for use in the head and neck region for safety reasons. Circumferential tape measures have become more commonly employed in clinical settings, though also have some limitations in respect to reliability (Michelotti et al., 2019). Despite this, tape measurements are the most used volumetric measures in HNL (Starmer, Cherry, et al., 2023). Perometry is another technique which uses an optical scanner to calculate limb volume. Though it has favorable reliability, (Deltombe et al., 2007), its cost has limited its application in standard clinical practice at this time.

2.6.2. Bioimpedance spectroscopy

Bioimpedance spectroscopy (BIS) uses resistance to an electrical current to establish the relative fluid content in a structure and has been used to measure the severity of lymphoedema. Different tissues resist electrical current in a predictable manner based on their conductive properties. For example, bone and fat tend to have high impedance whilst fluid is much more conductive (low impedance). Thus, BIS can differentiate the types of tissue most responsible for volumetric changes (Seward et al., 2016).

2.6.3. Radiographic measures of lymphoedema

Radiographic techniques have also been used in the assessment of lymphoedema. Magnetic Resonance Imaging (MRI) has been used to identify changes in dermal and subcutaneous structures related to lymphoedema (Sen et al., 2018). This has not, however been widely adopted in clinical practice, predominantly due to associated costs. In contrast, ultrasonography is portable, non-invasive, and low-cost and can provide information about the thickness and compliance of the dermal and subcutaneous tissues (Suehiro et al., 2016). Relatively good reliability has been shown when measuring skin to bone distances in the head and neck in normal individuals suggesting this may be a reasonable method for measuring lymphoedema (Piso et al., 2002).

2.6.4. Contrast-enhanced imaging

Imaging modalities may also be used to study lymphatic function. Indocyanine green (ICG) lymphography is one method used to study the superficial lymphatics (Aldrich et al., 2012). ICG can be injected subcutaneously or intradermally and then a near-infrared fluorescence camera can be used to map the movement of the dye as it is taken up by the initial lymphatics and then courses through the lymphatic system over time (Arie & Yamamoto, 2020). In contrast to ICG lymphography, lymphoscintigraphy can be used to assess both the superficial and deep lymphatic structures. As with lymphography, a radioactive dye is injected into the tissue and then the flow of the dye is captured using a scintillation camera (Munn & Padera, 2014). Lymphoscintigraphy can be used to identify missing lymphatic vessels, lymph nodes, and dermal backflow of lymph fluid based on contrast flow patterns. Although lymphoscintigraphy provides valuable information about the lymphatic system, costs, spatial resolution issues, and exposure to radioactive tracers limits its clinical utility.

2.6.5. Lymphoedema patient-reported outcomes

Patient reported outcome measures (PROMs) may be utilised to establish the impact of the oedema on the patient. A recent systematic review of studies reporting on lymphoedema specific PROMs identified 19 unique tools (Paramanandam et al., 2021). Eight tools were specific to upper extremity lymphoedema, three were specific to lower extremity oedema, and one to the head and neck. None of the PROMs identified were rated as sufficient across all nine properties of the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) framework (Mokkink et al., 2018). Content validity, or the degree to which an instrument measures the construct of interest, was surprisingly inadequate in 12 of 19 PROMs. For PROMs to be clinically meaningful, they must first and foremost reliably measure the construct of interest. One construct commonly measured using PROMs is patient perceived health-related quality of life (HRQoL).

2.7. Quality of life and health related quality of life

HRQoL has been increasingly embraced as an important consideration in clinical trials and in clinical management of patients with various health conditions. HRQoL as a concept is somewhat nebulous and its definition may vary according to context. Generally speaking, the World Health Organization’s definition of “health” is often used as the basic anchoring definition of HRQoL. This definition states that health is “a state of complete physical, mental, and social well-being and not merely the absence of disease.” (WHO, 1948) Thus, measures of HRQoL should encompass multiple dimensions including physical functioning, emotional functioning, and social well-being and functioning. HRQoL measures have been proposed as particularly salient in clinical trials meeting the following criteria (Gotay & Moore, 1992):

- HRQoL may be the primary endpoint in palliative trials.
- HRQoL may be a critical endpoint in trials where two treatments are anticipated to have parity of efficacy to identify the less toxic treatment option.
- HRQoL may be used to demonstrate any imbalance between small gains in cure/survival and increased toxicity of a treatment.
- In cases where short term outcomes are similar between two treatments, but long-term outcomes are poor, HRQoL may be an important way to distinguish the better treatment.

It is important to acknowledge that the terms “quality of life (QoL)” and “health-related quality of life (HRQoL)” are often used interchangeably though they represent distinct entities. Karimi & Brazier (2016) discuss how the overlap between QoL, HRQoL, and health status leads to some confusion in the literature. Whilst QoL is generally defined in terms of subjective overall well-being (Ferrans, 1990), HRQoL refers to “those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment” (Ebrahim, 1995). There are, however, other definitions of HRQoL which focus more on functional capacity, QoL excluding non-health related impacts such as sociopolitical impacts, and values associated with health status (Gold et al., 1996; Hays & Reeve, 2010; Torrance, 1987).

Karimi & Brazier (2016) argue that many measures that purportedly measure HRQoL are merely measures of perceived health status without any true reflection of QoL. Ferrans (1990) similarly acknowledges that measures are not always well-grounded/defined and that HRQoL measures must explicitly define what is meant by HRQoL. She categorises five primary definitions of HRQoL used in health science research: reference to normal life, happiness or satisfaction, capacity to achieve personal goals, social utility, and natural capacity. One concern with these categorisations is that many refer primarily to functional capacity without consideration of impact on the individual. Thus, some tools may not truly be measuring QoL.

It is critical when embarking on development of a tool that there are clear definitions regarding what the tool is meant to capture and how the developer is defining the underlying construct. The CALI-HaN is being developed as a measure of HRQoL focusing specifically on the impact this specific health condition has on well-being. This is consistent with Ebrahim's (1995) definition of HRQoL reflecting "those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment."

2.7.1. Models of overall quality of life

Several different models of QoL have been proposed over the past century. Calman's *Expectations* model of QoL (1984) suggests that quality of life is the difference between one's expectations and one's reality. Thus, the gap between expectations and reality may be the target for interventions to improve QoL. The *Needs-based* model suggests that QoL is related to the capacity to meet needs such as comfort, security, love, self-esteem, and rest (McKenna & Doward, 2004). The *Reintegration to Normal Living* model assumes some disruption in normal capacity, but the ability to do what one needs to do or desires to do, regardless as to health status (Wood-Dauphinee & Williams, 1987). Models of QoL will be discussed further in Chapter 4.

2.7.2. Influences on overall quality of life

Whilst the focus of this thesis is HRQoL related to HNL, it is important to acknowledge that QoL is malleable and may be influenced by numerous factors outside of a specific disease state, such as overall physical health, personality type, and psychological well-being (Blane et al., 2008; Culbertson et al., 2020; Hinz et al., 2019). Individual preferences may make certain contributions to QoL important at different times and at different life stages. For example, in early adulthood social interactions and intimacy may be more important to QoL than they may be in middle or late adulthood whereas pain, mobility restrictions, and independence may be more important in later adulthood (Alcaniz & Sole-Auro, 2018; Handa, Pereira, & Holmqvist, 2023). In addition to personal factors, systemic and societal factors may also impact an individual's QoL. Cheng et al. (2014) demonstrated that QoL was strongly influenced by parents' social class, education levels and current occupational levels, suggesting that individuals from lower socioeconomic backgrounds may have poorer QoL. Rylands et al. (2016) similarly found a relationship between HRQoL and deprivation in a population of patients with HNC. Thus, when considering QoL, we need to think not only of the symptoms relative to the disease state of interest, but also the personal and environmental contributors that may also influence QoL. This consideration is particularly relevant in the context of designing interventions to impact a patient's QoL.

2.7.3. Measuring quality of life and health-related quality of life

It is also important to emphasise that measuring QoL and HRQoL relies on information ascertained directly from the patient. Many studies have shown that clinician or caregiver reports of HRQoL differ significantly from that of the patient (Bjordal et al., 1995; Jensen et al., 2006). For example, anticipated symptoms of a treatment (e.g. taste changes) may be undervalued by professionals but highly impactful to patients. Similarly, clinicians may over-emphasise physical symptoms they perceive to be most important when estimating HRQoL. Thus, when interested in how a health condition impacts a patient's overall well-being, a PROM specific to HRQoL must be utilised.

2.8. Chapter summary

HNC prevalence is increasing, and survival rates are improving leading to an increased focus on survivorship issues. Treatment for HNC is often multimodal and usually includes either surgery, radiation, or both - with or without systemic agents. Multimodal treatment has been associated with a greater degree of short and long term toxicity and functional impairment. Dysphagia is a primary contributor to post HNC HRQoL and may be related to the development and severity of HNL. Most patients treated for HNC are at risk for development of HNL which may impact physical, emotional, and social function, thus interfering with QoL. Assessment of HNL, as a result, may require a multimodal assessment approach to include not only physical measures but also patient reported outcomes and experiences. Because some of the techniques for assessing lymphoedema may not be appropriate in the head and neck (such as water displacement tests), a core outcome set specific to HNL may be warranted. However, prior to determining what the core outcome measures may be, it is critical to first ascertain the state of the science in respect to HNL assessment. Chapter 3 presents the results of a systematic review performed to gain a better understanding of measures used in the assessment of HNL as well as the psychometric properties of those measures.

3. Assessment of Measures of Head and Neck Lymphoedema Following Head and Neck Cancer Treatment: A Systematic Review (Published paper)

3.1. Study rationale

Appropriate measurement of disease and health conditions is required to determine change over time, to establish therapeutic goals and appropriate interventions, and to measure the efficacy of treatments (deVet et al., 2018). Outcome measures are critical in clinical practice as well as in health outcomes research. It is essential that researchers and clinicians understand the available measures, their reliability, and their validity prior to utilisation. At times, core outcome sets may be warranted to comprehensively reflect complex conditions with multi-faceted impacts (Williamson et al., 2017).

Strategies used in the measurement of limb lymphoedema are not necessarily translatable to the head and neck region due to differences in physical structures as well as their physiologic functions. Identifying reliable and valid measurement tools is critical for the clinical management of HNL as well as for clinical outcomes research. Prior to publication of this systematic review, there were no prior systematic reviews specific to HNL assessment. To identify available measures specific to HNL and to assess their quality, reliability, and validity, I performed a systematic review of the literature.

3.2. Literature review

Review of existing research literature is an important step in understanding the state of the science on any topic. Literature reviews can be informal or conducted in a more rigorous way. To minimise bias when considering a body of literature, more rigorous reviews such as systematic reviews are recommended (Cook et al., 1997). Systematic reviews are among the methods used to interrogate available literature to synthesise what is known on a particular topic. They aim to identify all pertinent literature, summarise what is known, and assess the quality of the available evidence. Systematic reviews use "explicit and reproducible methods to systematically search, critically appraise, and synthesise on a specific issue…using strategies that reduce biases and random errors" (Gopalakrishnan & Ganeshkumar, 2013, p. 9).

3.2.1. Systematic reviews

Uman (2011) describes eight stages to the systematic review process.

1. The researcher must develop the review question, hypotheses, and establish the review title. At this stage the researcher should determine if a meta-analysis will be included as part of the systematic review. A meta-analysis is a statistical approach to combining the outcomes of a variety of publications to try to derive meaning from a body of existing literature.

2. Once the review question is well-established, the researcher then needs to define the inclusion and exclusion criteria for their review. This may include details about the (P)opulation to be studied, the types of (I)nterventions to be included, the (C)omparisons, and the (O)utcomes of interest (PICO). The types of studies that will be included in the review also need to be established a priori (e.g. randomised controlled trials only). Other variables such as time frame, languages, and types of data to be included should be determined in advance.
3. The search strategy needs to be developed. This should include all pertinent search terms related to the research question. Search criteria need to be specific enough to limit the number of studies needing to be reviewed, but broad enough to minimise the potential that important, relevant publications will be missed. In addition to searching online databases, hand searches of reference lists and key journals are often necessary.
4. Once publications have been identified through the search strategy, the research team needs to determine which studies meet the inclusion criteria. This is done through review of abstracts as well as full-text reviews. It is recommended that two reviewers review each article.
5. Once all publications have been reviewed for inclusion, key data points are extracted and recorded.
6. Study quality is assessed using available checklists according to the type of research being reviewed.
7. Results are analysed and interpreted. Where appropriate this may include statistical analyses such as meta-analyses. Where available data is inadequate

for quantitative analysis, descriptive analysis is instead provided with particular emphasis on summarising results and their implications for research and clinical practice.

8. Findings are disseminated through standard academic presentation and publication methods.

3.2.2. The Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist was initially published in 2009 (Liberati et al., 2009) and updated in 2020 (Page et al., 2021) to provide a quality checklist for systematic reviews. This statement proposes 27 items that should be included in systematic review reports. Figure 3-1 provides the specifics regarding each of the PRISMA recommendations. Consistent with best practice guidelines, I ensured the publication in section 3.7 followed these reporting guidelines prior to publication.

Figure 3-1 2020 PRISMA Guidelines (Page et al., 2021)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	

Section and Topic	Item #	Checklist item	Location where item is reported
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-	

Section and Topic	Item #	Checklist item	Location where item is reported
		regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj.n71

3.2.3. Measuring the quality of studies in a systematic review

Methods used to assess the quality of the studies reviewed vary according to the types of studies reviewed. To assess measurement tools reported in the literature, I selected the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist for reliability studies (Mokkink et al., 2018) and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for validation studies (Whiting et al., 2011).

The COSMIN risk of bias checklist for reliability studies allows an investigator to indicate whether each construct is rated as “excellent”, “good”, “fair”, or “poor” (Mokkink et al., 2018). The specific questions to rate are:

- Were patients stable in the time between the repeated measurements on the construct measured?
- Was the time interval between the repeated measurements appropriate?
- Were the test conditions similar for the repeated measurements?

- Did the professional(s) administer the measurement without knowledge of scores or values of other repeated measures in the same patient?
- Did the professional(s) assign scores without knowledge of the scores or values of other repeated measurement(s) in the same patient?
- Were there any other important flaws in the design or statistical methods of the study?
- For continuous scores: was an intraclass correlation coefficient (ICC) calculated?
- For ordinal scores: was a weighted kappa calculated?
- For dichotomous/nominal scores: was kappa calculated for each category?

The QUADAS-2 evaluates potential for bias in validation studies by assessing aspects of patient selection, index testing, reference standard, and flow and timing (Whiting et al., 2011). This allows a reviewer to determine if there are aspects of patient selection, test administration and interpretation, or patient flow that may introduce bias. Further, the QUADAS-2 questions help the researcher identify if there are concerns that the test being examined does not match the intent of the review being performed. Each parameter is rated as “yes,” “no,” or “unclear.” The specific parameters to rate are:

- Was the sample consecutive or random?
- Did the study avoid a case-control design?
- Did investigators avoid inappropriate exclusions?

- Were index test results interpreted without knowledge of the reference standard results?
- When an index test threshold is used, was it prespecified?
- Is the reference test likely to correctly identify the target condition?
- Was the reference standard determined without knowledge of scores on the index test?
- Was the time interval appropriate between administration of the index and reference tests?
- Did all participants receive the same reference standard?
- Were all participants included in analysis?

3.3. Reflections on study methods

The primary goal of my systematic review was to identify extant measures being used to assess, categorise, and grade HNL and to evaluate the quality of these measures. The overarching goal was to gain a better understanding of the state of this science to determine areas in need of development.

By using a systematic approach to the literature, I am confident that I identified most, if not all of the measures being used in HNL research. Given that this review was limited to English publications, there is a possibility that there may be instruments reported in the non-English literature. Additionally, it is possible that there are additional measures that are being used clinically, but not captured by a review of the scientific literature. Interestingly, within one year of my publication, two additional systematic reviews aimed at the same question were published (Arends et al., 2023; Fadhill et al., 2022). All three reviews identified a comparable cohort of measures and similarly concluded that most measures described in the literature have poor reporting on reliability and validity. Thus, this replication increased my confidence that my review was comprehensive, and my impressions of the available measures was appropriate.

A major challenge to applying tools to rate potential for bias in the measures identified in my review was that most measures did not have any formal validation. Thus, it was not possible to identify a single methodology for assessing instrument quality and risk of bias. To maintain a systematic approach despite inconsistency in instrument development, I selected two measures that have been used to assess risk of bias: the COSMIN criteria for reliability studies and the QUADAS-2 for validation studies. As most of the studies reported use of instruments that did not undergo formal validation and reliability testing, this was a limitation to our assessment of the instrument quality. For example, the QUADAS-2 was initially designed to be used in rating tests designed to diagnose a condition. Since none of the instruments were diagnostic for HNL, but rather descriptive of HNL, there could be some concern about using this quality assessment strategy. However, I feel that the COSMIN and QUADAS-2 criteria were the most appropriate for this review and provide at least some perspective as to the quality and potential bias of HNL instruments.

Typically, it is recommended that more than one reviewer perform data extraction during a systematic review. Given that this work was performed as part of a doctoral program, all data extraction was performed by a single reviewer. I acknowledge that this is a limitation that may increase the risk for bias in this literature review.

Fortunately, the similar conclusions reached by two independent research groups helps to validate the conclusions I reached.

Booth et al. (2016) suggest that systematic reviews performed as part of an advanced research degree have some different intents that those completed for other purposes. For example, they indicate that a student, through conducting a systematic review should be “sensitised to the influential researchers and research groups in the field” (p. 1970). Certainly, this was an important contribution to my learning. In completing this systematic review, I developed an increased awareness of the research group at Vanderbilt University which has dominated much of the literature on assessment of HNL (i.e. Jie Deng and Barbara Murphy among others). This group has employed superior methods for instrument development and validation. Based on my review of their work, I had the opportunity to reach out to Dr. Barbara Murphy to discuss my research ideas. Her feedback and insights were very valuable to decisions I needed to make regarding my own research.

3.4. How this study informed subsequent research

Whilst multiple opportunities for improvement were identified during this systematic review, the absence of a measure that took into consideration the impact of HNL on QoL stood out as a major shortcoming. As a clinical provider working with individuals with HNL, I have seen firsthand how patients and their caregivers are impacted by HNL. This is not just a matter of reduced mobility or difficulty working, but also includes substantial socioemotional consequences. As a result, I decided that development of a QoL specific PROM would be a worthwhile endeavor for my doctoral work. Those PROMs identified during my systematic review were examined in detail to understand what types of questions might be worthwhile for consideration during development of a new PROM.

3.5. Presentation and publication

3.5.1. Presentation

Head and neck lymphedema: How should we measure it? Starmer. H.M., Patterson, J., Cherry, M.G., Young, B., Fleming, J. (11/2021). Oral presentation at the American Speech Language Hearing Association Annual Convention, Washington, D.C.

3.5.2. Publication

Journal: Lymphatic Research and Biology

Status: Published

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Publication date: 16 February, 2023

Citation: Starmer, H., Cherry, M.G., Patterson, J., Young, B., Fleming, J. (2023) Assessment of Measures of Head and Neck Lymphedema Following Head and Neck Cancer Treatment: A Systematic Review. *Lymphatic Research and Biology*, 21(1):42-51. https://doi.org/10.1089/lrb.2021.0100

This paper was formatted in accordance with author guidelines provided by the journal *Lymphatic Research and Biology* (https://home.liebertpub.com/publications/lymphatic-research-and-biology/114/for-authors).

3.6. Contributions

Heather Starmer conceived and designed the study, established search criteria, completed searches, synthesised data, and drafted the manuscript under the supervision of Joanne Patterson, Jason Fleming, Gemma Cherry, and Bridget Young. Jason Fleming assisted with development of search criteria and participated in the review of abstracts and full-text articles. Joanne Patterson participated in full-text article reviews. Heather Starmer performed data extraction and tabulation. All authors contributed to development of the manuscript and approved the final article.

3.7. Published paper

(Reprinted from Lymphatic Research and Biology. Volume 21, Issue 1. Starmer et al., Assessment of Measures of Head and Neck Lymphedema Following Head and Neck Cancer Treatment: A Systematic Review. Pp. 42-51. 2023. With Permission from Mary Ann Liebert, Inc.)

Assessment of measures of head and neck lymphedema following head and neck cancer treatment: a systematic review

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Abstract

Purpose: Head and neck lymphedema is a common condition following head and neck cancer (HNC) treatment, with substantial functional morbidity. This systematic review aimed to i) identify tools used to assess head and neck lymphedema in HNC patients and ii) determine their validity and reliability.

Methods: Electronic and hand searches of Prospero, Medline, Cochrane Library and Embase; searched from their inception until April 2021 and hand searches were independently screened by two reviewers. Studies were included if they were available in English and measured lymphedema in adult HNC patients (aged ≥18 years). Data including psychometric characteristics were extracted and synthesized narratively, with QUADAS-2 and COSMIN checklists used to assess risk of bias.

Results: Thirty-three studies, reporting 38 assessment tools, were included. Assessments included clinician rating scales, symptom inventories, size measures, measures of internal edema, radiographic and ultrasonographic measures, and quality of life measures. Of the 38 measures cited, only 11 had any degree of validation and reliability testing. Risk of bias varied among the different assessment tools.

Conclusion: While many tools are used in the assessment of head and neck lymphedema, the majority of these tools lack validation and reliability data. Only one tool, the Head and Neck Lymphedema and Fibrosis Symptom Inventory, met criteria for strong quality assessment. Further efforts to establish a core set of metrics for this complex condition are warranted.

Introduction:

Head and neck lymphedema (HNL) is an increasingly recognized contributor to post head and neck cancer (HNC) functional impairment and occurs in up to 90% of HNC survivors [1-3]. Lymphedema may occur due to obstruction of the lymphatic channels due to tumor, scar, or fibrosis, removal of lymph nodes and vessels during surgical resection, or damage to the lymphatic structures commonly noted following radiation therapy [4]. The result of this damage is the accumulation of protein-rich lymphatic fluid in the interstitial space. This edema may result in compressive symptoms, reduced mobility, inflammation, and fibrosis, all of which may contribute to functional impairment such as substantial dysphagia, trismus, and dysphonia [1, 5].

Lymphedema may occur internally in structures such as the larynx and pharynx or externally in structures of the face and neck. In the early stage of lymphedema development, there may not be visible evidence of edema, however the patient may report a sense of fullness or tightness [6]. As the lymphedema advances, soft edema may be noted in the face, submental region, or neck. If left untreated, this may progress to a point of hard swelling, an indicator of development of fibrotic tissue [1, 3]. Post-radiation fibrosis has been implicated as a primary contributor to development of dysphagia, trismus, and cervical dystonia – key determinants of quality of life (QOL) in HNC survivors [7-11]. It is critical to identify lymphedema early and to provide treatments to minimize the development of chronic, potentially debilitating edema [12]. Further, there is need to better understand the trajectory of HNL over time. As such, establishing a reliable, stable, and valid battery of HNL assessment tools is a critical need for both clinicians and researchers.

Diagnosis of lymphedema is typically based on physical examination and clinical history [13]. There is no extant diagnostic tool for HNL. Rather there are a number of tools used to describe or measure lymphedema and its impact on patients [14]. Given the importance of accurate diagnostic and measurement tools in determining changes in response to treatment, this systematic review sought to determine: i) what tools are currently used in the assessment of HNL; and ii) their overall reliability and validity.

Methods:

Conduct and Reporting

The conduct and reporting of this systematic review adhere with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15] and was registered on PROSPERO, an international prospective register of systematic reviews on 13 May 2021 (database number CRD42021252001).

Search Strategy

Electronic and hand searches were used to identify relevant studies. Prospero, Medline, Cochrane Library, clinicaltrials.gov, and Embase were searched from their inception until April 2021 using syntax combining synonyms for lymphedema, head and neck, and measurement and Medical subject heading (MeSH) terms (Table 1). This was conducted between 16 April 2021 and 1 July 2021. The reference lists of included studies and relevant reviews were searched for additional relevant literature.

Table 1 Search terms

Concept	Synonym	MeSH	Syntax
Lymphedema	Edema [TW] Lymphedema [TW] Edema [TW] Lymphedema [TW]	“Lymphedema” [MH]	(“Lymphedema” [MH] OR Lymphedema [TW] OR Edema [TW] OR Edema [TW] OR lymphedema [TW])
Head and Neck	Head Neck	“Head” [MH] “Neck” [MH]	(“Head” [MH] OR “Neck” [MH] OR “Head” [TW] OR “Neck” [TW])
Measurement	Clinician-reported outcome measure Patient-reported outcome measure Tape measure	“Reproducibility of Results” [MH] “Symptom Assessment” [MH]	(“Reproducibility of Results” [MH] OR “Symptom Assessment” [MH] OR “symptom assessment” [TW] OR “patient reported outcome measure” [TW] OR “patient reported outcome measures” [TW] OR “Clinician-reported outcome” [TW] OR “Clinician-reported outcomes” [TW] OR “Tape measure” OR “Tape measurement”[TW])

Screening and Selection

Search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) and screened for eligibility. Two reviewers (HS, JF) independently reviewed all abstracts. Discrepancies between raters were addressed through discussion and consensus. The full text of potentially relevant studies was reviewed independently by two of three reviewers (HS, JF, JP) and a third reviewer in instances where there were disagreements about inclusion. Studies were included if they were available in English and measured lymphedema in adult HNC patients (aged ≥18 years). Primary source study designs were included, however reviews and opinion pieces were not included but their references were hands-searched for relevant articles.

Data Extraction, Quality Assessment and Risk of Bias

One reviewer (HS) extracted relevant data (study details, population studied, the type of measure(s) reported, specific measures used, and psychometric properties of the measures when available) using a data extraction tool developed for this review. Risk of bias for each tool was evaluated by one reviewer (HS) using the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) risk of bias checklist for reliability studies [16] and Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [17] for validation studies. COSMIN risk of bias assessment of reliability studies is described in the User Manual [16] and includes assessment of patient stability between measures, time interval between measures, similarity of measurement conditions, administration of measurements, score assignment, other important flaws, and use of preferred statistical methods. Each property is rated using a 4-point scoring system indicating whether the measure meets the standard "very good," "adequate," "doubtful," or "inadequate". The QUADAS-2 tool [17] evaluates potential for bias in validity studies by assessing aspects of patient selection, index testing, reference standard, and flow and timing. Each question within each parameter is rated as "yes," "no," or "unclear." Data were tabulated and synthesized narratively. HNL assessment tools were classified according to the following categories: clinician rating scales, patient reported symptom scales, tape measurement strategies, radiographic measures, ultrasonographic measures, measures of internal edema, and quality of life ratings. Tools that did not fit into these categories were classified as “other”.

Results:

The searches identified 152 reports/articles, leaving 149 following de-duplication. Screening of 149 article abstracts resulted in identification of 58 studies for full text review (Figure 1). Following full text review, 33 articles, reporting 38 measurement tools, were included in the review (Table 2-3).

Figure 1 PRISMA flowchart

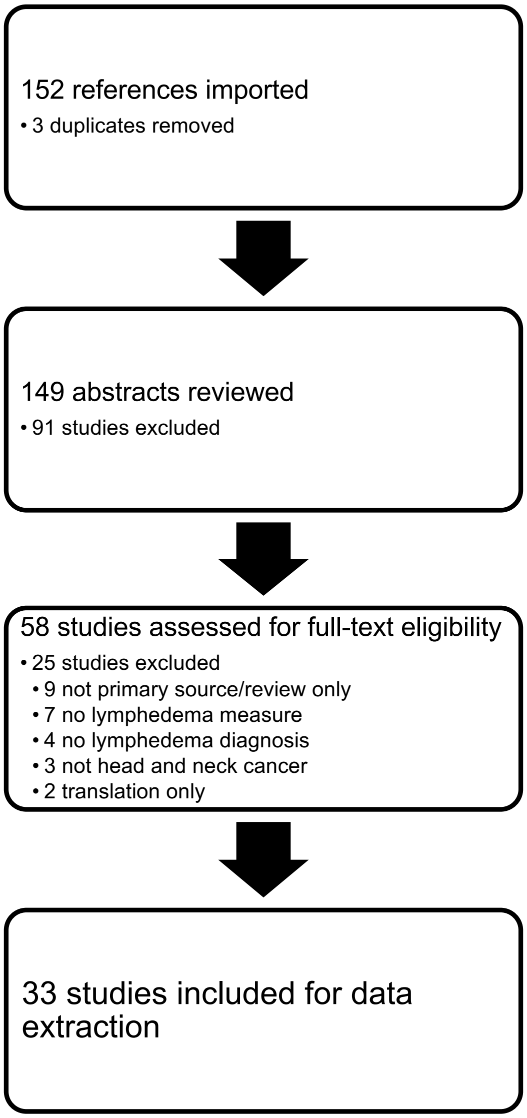

Table 2 Characteristics of lymphedema measures

Category of measure	Measure and studies citing	Description of measure	# of items	# of studies citing	Reliability testing (HNL)	Validity testing (HNL)
Clinician rating	MD Anderson Lymphedema Severity Scale [8, 18-22]	5-point severity scale	1	6	No	No

	Foldi's scale [1-2, 23-25]	4-point severity scale	1	5	No	No
	CTCAE rating [3, 23]	5-point severity scale	1	2	No	No
	ACS lymphedema scale [3, 23]	4-point severity scale	1	2	No	No
	HN-ELAF [26]	5-point severity scale	1	1	Yes	Yes
	Qualitative analysis [27]	Qualitative analysis	3	1	No	No
	Clinician perception of severity [28]	5-point rating scale	1	1	No	No
	Micke Scale [25]	5-point clinical classification	5	1	No	No
Symptom scoring	LSIDS-HN [29-33]	Patient perceived lymphedema and fibrosis symptoms	48	5	Yes	Yes
	HN-LEF Symptom Inventory [29]	Patient perceived lymphedema and fibrosis symptoms	33	1	Yes	Yes
	Vanderbilt Head and Neck Symptom Survey [2, 33]	Patient perceived symptom survey	50	2	No	No
	Derriford Appearance Scale [28, 34]	Psychological distress related to aesthetic deformity	59	2	No	No
	Modified Blepharoplasty Outcome Evaluation [28, 34]	Self-perception of appearance	5	2	No	No
	Tactile medical score [35]	5-point Likert rating	5	1	No	No
	Intensity of tension [22]	10-point VAS	1	1	No	No

	Smith method [36]	Clinician reported symptoms	undefined	1	No	No
Size measures	MDACC tape measures [20, 22, 37-39]	Facial and neck measures	10	5	No	No
	ALOHA tape measures [19, 21]	Facial and neck measures	4	2	Yes	Yes
	Ayestaray method [27]	Head circumference	3	1	No	No
	Piso method [36]	Facial measures	5	1	No	No
	Tacani method [40]	Facial and neck measures	11	1	No	No
Internal edema	Patterson Scale [1-3, 8, 18, 30, 41]	Endoscopic rating of internal lymphedema	13	7	Yes	Yes
	Revised Patterson Scale [33, 42]	Endoscopic rating of internal lymphedema	9	2	Yes	Yes
	Maximal IL severity [8]	Endoscopic rating of internal lymphedema	2	1	No	No
	LENT-SOMA [25]	Breathing difficulties and internal lymphedema	3	1	No	No
Radiographic	LE score [43]	Grading of CT scans	2	1	No	Yes
	CT-LEFAT [44]	Grading of CT scans	3	1	No	Yes
	Turcotte method [45]	Grading on fluoroscopy	3	1	No	No
Ultrasound	Vanderbilt method [31]	Skin to internal structure distance	10	1	No	No
	Piso method [36, 46]	Skin to bone distance	3	2	Yes	Yes

Quality of life	Lymphedema QOL Inventory [32]	Lymphedema related QOL	45	1	No	No
	Micke VAS [25]	QOL rated by VAS	1	1	No	No
	Vanderbilt VAS [33]	5-item QOL VAS	5	1	No	No
Other	Goniometer [33, 37]	Neck ROM	6	2	No	No
	Moisture Meter D [19, 21]	Tissue dielectric content	3	2	Yes	Yes
	Near-infrared fluorescence [38]	Dermal backflow	1	1	No	No
	3-D Volume analysis [20]	3-D surface scanning and volume measures	1	1	No	No
	Vanderbilt photo rating scale [33]	30 segment grid analysis of pictures	1	1	No	No

Table 3 Details regarding studies included in data extraction

Citation	Country	# of participants	% male	Mean age	Ethnicity (% white)	Type of cancer treatment	Type of cancer	Quality rating
Ozdemir, 2021[20]	Turkey	21	76	57	Not reported	All	OC, LX, Thyroid, Parotid	II
Jeans 2020 [18]	Australia	62	89	61	Not reported	74% CRT 26% PORT	OC, OP (69%), LX, HP	II
Starmer 2021 [42]	USA	7	Not reported	Not reported	Not reported	Not reported	Not reported	II
Doke 2018 [37]	USA	34	88	57	97	53% PORT 47% XRT	OC (20%), OP (70%), LX (9%)	II

Patterson 2007 [41]	UK	23	Not reported	Not reported	Not reported	XRT	All	II
Piso 2002 [46]	Germany	21	38	20-45	Not reported	Not reported	Not reported	III
Turcotte 2018 [45]	USA	40	60	58	Not reported	CRT	OC, OP	II
Deng 2021 [29]	USA	117	84	59	94	All	OC, OP	I
Jeans 2021 [8]	Australia	79	94	61	Not reported	CRT & PORT	OC, OP, LX, HP	II
Ridner 2020 [32]	USA	72	67	60	90	Not reported	Not provided	I
Gutierrez 2020 [35]	USA	205	74	60	Not reported	All	Primarily OC and OP	III
Akashi 2018 [43]	Japan	95	59	69	Not reported	100% Surgery 23% PORT	OC	III
Alamoudi 2018 [34]	Canada	20	85	65	Not reported	XRT/CRT 56% PORT 46%	OP, LX, neck, NC, OC	III
Aulino 2018 [44]	USA	20	Not reported	Not reported	Not reported	XRT	All	II
Ayestaray 2013 [27]	France	4	50	62	Not reported	Surgery	OC	II
Brake 2014 [28]	Canada	9	66	60	Not reported	XRT =/- surgery	LX (33%), OP (33%), NP (11%), OC (11%), UKP (11%)	II
Deng 2016 [31]	USA	51	78	57	94	All	All	II
Deng 2013a [1]	USA	103	69	60	89	All	All	III
Deng 2013b [23]	USA	103	69	60	Not reported	90% at least 2 modalities	Not reported	II

Deng 2012a [24]	USA	81	71	60	89	All	All	II
Deng 2012b [30]	USA	48	79	61	93	All	All	II
Deng 2015b [26]	USA	30	73	60	90	All but no surgery only	All but no HP, sinus, or salivary	II
Gutierrez 2019 [38]	USA	10	90	65	100	70% XRT 30% PORT	Not reported	II
Jackson 2016 [2]	USA	81	77	59	95	All	Mostly OP and OC	II
Mayrovitz 2018 [39]	USA	44	77	61	94	XRT +/1 surgery, chemo	Not reported	III
Micke 2003 [25]	Germany	36	Not reported	Not reported	Not reported	XRT +/- surgery, chemo	Not reported	III
Nixon 2014 [19]	Australia	8	88	62	Not reported	XRT +/- surgery, chemo	Not reported	III
Piso 2001 [36]	Germany	18	78	60	Not reported	Surgery with ND	OC	III
Purcell 2016 [21]	Australia	20	85	61	Not reported	95% XRT 55% chemo 29% surgery + CRT	Not reported	II
Ridner 2021 [33]	USA	43	81	62	98	Not reported	Not reported	II
Ridner 2016 [3]	USA	83	72	58	90	42% induction CRT, 17% CRT 29% PORT	All	I
Smith 2015 [22]	USA	1202	78	61	80	58% PORT	All	III

Tacani 2016 [40]	Brazil	20	80	54	Not reported	Surgery +/- XRT chemo	All	III

Key: CRT – chemoradiotherapy; PORT – post-operative radiation therapy; XRT – Radiation therapy; OC – oral cavity; OP - oropharynx, LX – larynx; HP – Hypopharynx; NP – Nasopharynx; UKP – unknown primary

Eight categories of measures were distinguished: clinician rating scale (n=8), symptom scoring (n=6), tape measures (n=5), internal edema (n=4), radiographic measures (n=3), quality of life (QOL) tools (n=3), ultrasonographic measures (n=2), and other (n=5). Of the 38 tools identified, only 11 had any degree of validation or reliability data available. Forty-five percent of studies (n=15) reported on using three or more measuring tools.

Clinician rated HNL measures

Clinician rated measurements were most frequently reported and were present in 19 (58%) of included studies. Three of the clinician measures were specific to a single publication without any replication or validation [25, 27-28]. Of the remaining five tools, Foldi's scale and the MD Anderson Head and Neck Lymphedema Grading Scale (adapted from Foldi's scale) were most common, cited in 11 studies (33%) [1-2, 8, 18-25]. The primary difference between the Foldi scale and the MD Anderson scale is the division of stage 1 lymphedema into 1a and 1b which refer to soft, non-pitting edema versus reversable pitting edema respectively. Despite being frequently used, neither of these scales have undergone formal validation or reliability testing. Only the Head and Neck- External Lymphedema and Fibrosis scale (HN-ELAF) [26] reported any validation or reliability data. This grading system is a 5-point severity scale of external HNL and fibrosis developed in conjunction with an expert panel taking into consideration the conceptual framework, strengths and weaknesses of existing assessment criteria, and revisions of the tool in response to preliminary testing. Inter-rater reliability was strong with 83% exact agreement between raters (100% agreement within 1 grade), kappa = 0.75, and concordance correlation coefficient=0.91.

HNL symptom assessment

Patient reported symptom assessment was reported in 45% (n=15) of included studies. Three of the symptom scales were previously validated in other populations but had not undergone validation in patients with HNL [2, 28, 33-34]. The Lymphedema Symptom Intensity and Distress Survey Head and Neck (LSIDS-HN) [29-33] was the most frequently cited head and neck lymphedema symptom survey (33%), and the revised version, Head and Neck Lymphedema and Fibrosis Symptom Inventory, (HN-LEF) [29] accounted for an additional 7% of symptom surveys reported. This scale was the only symptom survey specific to HNL with validation data. Internal consistency was favorable at the end of treatment and 3 months post-treatment for the HN-LEF symptom clusters soft tissue and neurologic toxicity (Cronbach's 0.86 -0.90), body image and sexuality (Cronbach's alpha 0.75 - 0.90), systemic symptoms and social functioning (Cronbach's alpha 0.69 - 0.78), swallowing and taste change (Cronbach's alpha 0.69-0.80), communication (Cronbach's alpha 0.71-0.80), and jaw and oral dysfunction (Cronbach's alpha 0.59-0.76). The cluster for mucosal irritation had lower internal consistency (Cronbach's alpha 0.49-0.73). The high prevalence and severity range of symptoms supported content validity and the authors indicated additional psychometric testing is underway.

Tape measures of HNL

Only 30% of studies included any measure of structure size [19-22, 27, 36-40]. Five different tape measurement systems were reported, the most frequently cited being the MD Anderson approach, which accounted for 50% of studies measuring head and neck structures [20, 22, 37-39]. This method measures 7 distances between structures on the face as well as three circumferential neck measures. Though frequently used, none of the studies using this method provided reliability data. Only the Assessment of Lymphedema of the Head and Neck (ALOHA) approach provides any data on reliability [19-21]. Interrater reliability was excellent for 3 of the 4 tape measurements (ICC > 0.90) with poorest reliability noted for the measurement between the lip and lower neck (ICC=0.420). This method also provides clear instructions on a standardized measurement protocol to measure neck circumference in two locations as well as submental girth from ear to ear.

Internal lymphedema measures

One third of included studies attempted to rate internal lymphedema using endoscopic assessment [1-3, 8, 18, 25, 30, 33, 41-42]. The Patterson Scale and the Revised Patterson Scale accounted for 82% of studies reporting on internal lymphedema [1-3, 8, 18, 30, 33, 41-42]. Both scales provide reliability data, with improved reliability noted with the Revised Patterson Scale (Overall weighted kappa=0.54 for the original scale and 0.64 for the revised scale). The revised scale provides in-depth instructions for exam protocol as well as interpretation.

Radiographic and ultrasonographic measures

Radiographic and ultrasonographic measures were infrequently reported in only 18% of included studies [31, 36, 43-46]. Two reported measures on CT scans [43-44], two on ultrasound [31, 36, 46], and one on videofluoroscopy [45]. These measures attempt to provide quantitative assessment of tissue changes related to lymphedema. The CT-LEFAT and videofluoroscopic rating strategy both included measures of the epiglottis and posterior pharyngeal wall. Both CT measures looked at characteristics of fat stranding as a marker of lymphedema. Both CT measurement tools were able to demonstrate changes in radiographic measures of lymphedema over time supporting face validity, however further validation and reliability for these scales is not currently available. The videofluoroscopic measures described by Turcotte [45] demonstrated excellent inter- (ICC values ranged from 0.87 -1.00) and intra-rater reliability (ICC values ranged from 0.96-0.98). Measures of the posterior pharyngeal wall in particular were sensitive to change over time but did not correlate with measures of swallowing ability [45].

Quality of life measures

In respect to QOL measures, while three studies (9%) reported patient-related QOL [25, 32-33], two used non-validated visual analog scales (VAS) [25, 33]. Neither study using VAS provided details regarding what questions were asked regarding QOL. The remaining instrument (LyQLI) [32] was validated in the broader lymphedema population, but not specifically in patients with HNL. While patients with HNL may have been part of the validation set, the authors combined upper extremity and head and neck lymphedema and did not provide further breakout. Thus, it is possible very few HNL patients were included in the validation of the LyQLI.

Other measures

Finally, several other tools were cited in these studies that did not fit into any of the aforementioned categories [19-21, 33, 37-38]. Of those measures, only the Moisture Meter-D (MMD) [19, 21], which measures tissue dielectric content, had any data on validity and reliability. Inter- and intra-rater reliability for the MMD were excellent with intraclass correlation coefficients of 0.973 and 0.974 respectively. Further, the MMD was able to distinguish between those with lymphedema and healthy controls ($p<0.001$). Other measures such as near-infrared fluorescence and 3-D volume analysis show promise in lymphedema assessment, however, are in their relative infancy in respect to development of standardized protocols.

Psychometric properties

Psychometric properties were extracted for the 9 measures that had been studied in patients with HNL (Table 4) The most robust validation was seen in the development of the LSIDS-HN and its revision the HN-LEF Symptom Inventory. Good reliability was reported for the ALOHA tape measuring method, the HN-ELAF scale, the Piso ultrasound method, and the Moisture Meter D. While the initial Patterson Scale had poor reliability for some ratings, the Revised Patterson Scale effectively addressed those issues yielding improved scale reliability.

Table 4 Psychometric properties

Measure	Content validity	Face validity	Construct validity	Structural validity	Hypothesis testing	Criterion validity	Internal consistency	Reliability
LE score	?	+	NR	NR	?	NR	NR	NR
CT-LEFAT	+	+	NR	NR	NR	NR	NR	NR
ALOHA	+	+	NR	?	NR	NR	NR	+
HN-ELAF	+	+	+	?	NR	NR	NR	+
LSIDS-HN / HN-LEF	+	+	+	+	+	+	+	NR
Piso ultrasound	-	+	NR	NR	NR	NR	NR	+
Patterson scale	+	+	+	NR	NR	NR	NR	+/-
Revised Patterson scale	+	+	+	NR	NR	NR	NR	+
Moisture Meter D	+	+	+	NR	NR	+	NR	+

Key: NR = Not reported; + = acceptable; - = unacceptable; ? = unable to assess

Risk of bias assessment

Quality and risk of bias were assessed in those tools with validation or reliability data. Table 5 provides the COSMIN checklist for the seven measures that had reliability testing and Table 6 provides the QUADAS-2 risk of bias assessment for eleven validation studies. Of the measures cited, the HN-LEF Symptom Inventory provided the highest quality and lowest risk of bias. Multiple measures (CT-LEFAT, Piso ultrasound, and Patterson scale) did not include a reference standard in their validation studies.

Table 5 COSMIN checklist for risk of bias in reliability studies

Measure	Patients stable between measures?	Appropriate interval between measures?	Conditions similar between measures?	Measures administered without knowledge of other measures?	Scores assigned without knowledge of prior scores?	Other flaws ?	ICC if continuous?	Kappa if ordinal ?
ALOHA	n/a	Adequate	Adequate	Very good	Very good	Very good	Very good	n/a
HN-ELAF	n/a	Doubtful	Adequate	Very good	Very good	Very good	n/a	Very good
Piso ultrasound	Very good	Very good	Very good	Doubtful	Doubtful	Very good	Very good	n/a
Patterson	n/a	Very good	Very good	Adequate	Adequate	Very good	n/a	Very good
Revised Patterson	n/a	Adequate	Very good	Adequate	Adequate	Very good	n/a	Very good
Lymphedema QOL	Very good	Very good	Very good	n/a	n/a	Very good	Very good	n/a
Moisture Meter D	Very good	Adequate	Very good	Adequate	Adequate	Very good	Very good	n/a

Key: n/a= not applicable

Table 6 QUADAS-2 risk of bias assessment for validation studies

Measure	**Risk of bias**				**Applicability concerns**		
	Pt selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
LE score	High risk	High risk	n/a	Unclear	High risk	Low risk	n/a
CT-LEFAT	Low risk	Low risk	n/a	Low risk	Low risk	Low risk	n/a
ALOHA	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
HN-ELAF	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear
DASS	Low risk	Low risk	n/a	Low risk	High risk	Low risk	n/a
LSIDS-HN / HN-LEF	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Piso ultrasound	Low risk	Low risk	n/a	Low risk	Low risk	Low risk	n/a
Patterson scale	Low risk	Low risk	n/a	Low risk	Low risk	Low risk	n/a
Revised Patterson scale	Low risk	Low risk	n/a	Low risk	Low risk	Low risk	n/a
Lymphedema QOL	Low risk	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear
Moisture Meter D	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Key: n/a- not applicable

Discussion:

This systematic review aimed to identify tools used to assess HNL in HNC patients and to determine the validity and reliability of these tools. Thirty-eight different tools were identified, which encompassed a variety of constructs including patient symptoms, clinician severity ratings, size of internal and external structures, and QOL. Most studies included more than one tool, suggesting that assessment of lymphedema likely requires a set of complementary measures to establish a comprehensive view of HNL and its impact on the patient. The variety of assessment tools employed across studies suggests there is limited agreement regarding the most suitable tool or set of tools to evaluate this condition. Further, the lack of validation and reliability data for many reported assessment tools raises greater concerns, particularly in the context of treatment efficacy studies. Clearly, there is a need to optimize validation of assessment tools and to develop a core set of metrics that may comprehensively assess HNL.

There are challenges inherent to volumetric and size measures of HNL. Unlike the limbs, the head and neck region is not a cylindrical structure that can be easily circumferentially measured, nor can it be submerged in water to obtain displacement measures of volume. Whereas size measurements are the mainstay of assessing limb lymphedema, challenges in measuring the head and neck region are reflected in the fact that only 30% of studies included any evaluation of structure size. These challenges are highlighted by the paucity of valid, reliable measures HNL. The ALOHA method was designed specifically to address concerns around reliability and provides standardized set up and measurement criteria. While their study demonstrated good reliability for 3 of the 4 measurements, it does not provide measurement of facial edema, which can be an important issue for some patients with HNL. The MD Anderson tape measure strategy does assess both facial and neck edema, however reliability has not been assessed in any of the studies that use it. Because of the topographic challenges of measuring an irregular structure like the face, it is particularly critical to establish reliable measurements using this or other scales.

Symptom inventories provided primary insight into the patient perspective, with no HNL-specific QOL scale identified. The HN-LEF Symptom Inventory provides a robust tool to capture patient symptoms and the severity of their concern about each symptom. This scale includes 33 items grouped into 7 clusters including soft tissue/neurologic toxicity, systemic symptoms and social functioning, jaw, and oral dysfunction, swallowing and taste changes, body image and sexuality, communication, and mucosal irritation. Indeed, it was the only HNL-specific patient reported outcome measure cited in the recent systematic review of lymphedema-specific patient reported outcome measures (PROMs) [47]. In contrast, seven PROMs were identified specific to upper limb lymphedema. This highlights the need for further development of HNL-specific, high-quality PROMs.

The majority of studies reporting on internal lymphedema utilized either the Patterson Scale or the Revised Patterson Scale. Most studies reported the severity levels of internal edema as defined in the Patterson Scale, while one study used the highest grade noted on the Patterson Scale as well as the total number of structures with edema to quantify overall severity. This particular method of interpreting the Patterson Scale has not been validated but may be worthy of future validation efforts.

Finally, there are multiple emerging, novel methods for assessing head and neck lymphedema through radiographic imaging, ultrasound, near-infrared fluorescence, and 3-D image analysis. While there is emerging evidence regarding potential validity and reliability of these measures in lymphedema at large, their uptake in HNL has been limited to date.

As with all studies, there are limitations that need to be acknowledged in this review. First, exclusion of studies in languages other than English may have prevented us from identifying other tools in use across the globe. Additionally, there is potential that publication bias prevented consideration of tools that have not yet been published at the time of this review. While abstract and full text reviews were performed by multiple reviewers, extraction of quality and risk of bias data was performed by a single individual. While this may potentially introduce bias, the reviewer is a clinician-investigator acutely involved in research and clinical management of patients with HNL, thus providing familiarity and expertise in the review of this literature. Despite these limitations, this systematic review provides valuable insight into the state of the science in HNL and brings the strength of a multidisciplinary study team including speech language pathology, psychology, and head and neck surgery.

Conclusions:

Head and neck lymphedema is generally diagnosed based on clinical history and physical examination. Measurement of this condition relies on a selection of tools that can be used to describe or quantify lymphedema and the impact it may have on patients. Unfortunately, most of the measures that have been reported in the HNL literature and used clinically have no validation or reliability data. Thus, clinicians and researchers need to be mindful of using these measures to document change. The HN-LEF Symptom Inventory was the most thoroughly validated measure specific to patients with HNL and it has undergone rigorous testing and revision. It appears to be an appropriate addition to the assessment battery of head and neck lymphedema clinicians. Additional physical measures such as those obtained during imaging or clinical examination should be used to complement the patient perspective but may require additional validation. Due to the complexity of HNL and its impact on function and patient outcomes, a multi-factorial method for assessment appears appropriate, though the exact composition of that test battery is not yet established. Further efforts to establish a validated core set of HNL metrics are warranted.

References:

1. Deng J, Ridner SH, Dietrich MS, Wells N, Murphy BA. Assessment of external lymphedema in patients with head and neck cancer: a comparison of four scales. Oncol Nurs Forum. (2013a). 40(5):501-6. https://dx.doi.org/10.1188/13.ONF.501-506
2. Jackson LK, Ridner SH, Deng J, Bartow C, Mannion K, Niermann K, et al. Internal Lymphedema Correlates with Subjective and Objective Measures of Dysphagia in Head and Neck Cancer Patients. Journal of Palliative Medicine. (2016). 19(9):949-56. https://dx.doi.org/10.1089/jpm.2016.0018
3. Ridner SH, Dietrich MS, Niermann K, Cmelak A, Mannion K, Murphy B. A Prospective Study of the Lymphedema and Fibrosis Continuum in Patients with Head and Neck Cancer. Lymphat. (2016). 14(4):198-205. https://dx.doi.org/10.1089/lrb.2016.0001

4. McGarvey AC, Osmotherly PG, Hoffman GR, Chiarelli PE. Lymphedema following treatment for head and neck cancer: impact on patients, and beliefs of health professionals. Eur J Cancer Care (Engl). (2014). 23(3):317-327. doi:10.1111/ecc.12134
5. Murphy, B. A., & Ridner, S. Late-effect laryngeal edema/lymphedema. J Lymphedema, (2010). 5, 92–93.
6. Smith BG, Lewin JS. Lymphedema management in head and neck cancer. Curr Opin Otolaryngol Head Neck Surg. (2010). 18(3):153-158. doi:10.1097/MOO.0b013e32833aac21
7. Stubblefield MD. Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. PM R. (2011). 3(11):1041-1054. doi:10.1016/j.pmrj.2011.08.535
8. Jeans C, Ward EC, Brown B, et al. Association between external and internal lymphedema and chronic dysphagia following head and neck cancer treatment. Head Neck. (2021). 43(1):255-267. doi:10.1002/hed.26484
9. Nachalon Y, Nativ-Zeltzer N, Evangelista LM, et al. Cervical Fibrosis as a Predictor of Dysphagia. Laryngoscope. (2021). 131(3):548-552. doi:10.1002/lary.28880
10. King SN, Dunlap NE, Tennant PA, Pitts T. Pathophysiology of Radiation-Induced Dysphagia in Head and Neck Cancer. Dysphagia. (2016). 31(3):339-351. doi:10.1007/s00455-016-9710-1

11. Fu MR, Kang Y. Psychosocial impact of living with cancer-related lymphedema. Semin Oncol Nurs. (2013). 29(1):50-60. doi:10.1016/j.soncn.2012.11.007
12. Foldi MD, Foldi E, Strossenreuther RHK, Kubik S. Foldi's Textbook of Lymphology: for Physicians and Lymphedema Therapists, 2012, Third ed. Elsevier Urban & Fischer Verlag, Muchen, Germany.
13. Rockson SG, Keeley V, Kilbreath S, Szuba A, Towers A. Cancer-associated secondary lymphedema. Nat Rev Dis Primers. (2019). 5:22. doi: 10.1038/s41572-019-0072-5
14. Deng J, Ridner SH, Aulino JM, Murphy BA. Assessment and measurement of head and neck lymphedema: state-of-the-science and future directions. Oral Oncol. (2015a0. 51(5):431-437. doi:10.1016/j.oraloncology.2015.01.005
15. Moher D, Lierati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analysis: The PRISMA statement. Ann Intern Med. (2009). 151 (4): 264-9.
16. LB Mokkink, M Boers, CPM van der Vleuten, LM Bouter, J Alonso, DL Patrick, HCW de Vet, CB Terwee. COSMIN Risk of Bias tool to assess the quality of studies on reliability or measurement error of outcome measurement instruments: a Delphi study. BMC Medical Research Methodology. (2020). 20(293).
17. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. (2011). 155(8):529-536. doi:10.7326/0003-4819-155-8-201110180-00009

18. Jeans C, Brown B, Ward EC, Vertigan AE, Pigott AE, Nixon JL, et al. Comparing the prevalence, location, and severity of head and neck lymphedema after postoperative radiotherapy for oral cavity cancers and definitive chemoradiotherapy for oropharyngeal, laryngeal, and hypopharyngeal cancers. Head Neck. (2020). 42(11):3364-74. Doi: 10.1002/hed.26394
19. Nixon J, Purcell A, Fleming J, McCann A, Porceddu S. Pilot study of an assessment tool for measuring head and neck lymphedema. Br J Community Nurs. (2014). Suppl: S6, S8-S11.
20. Ozdemir K, Keser I, Duzlu M, Erpolat OP, Saranli U, Tutar H. The Effects of Clinical and Home-based Physiotherapy Programs in Secondary Head and Neck Lymphedema. Laryngoscope. (2021). 131(5): E1550-E7. Doi: 10.1002/lary.29205
21. Purcell A, Nixon J, Fleming J, McCann A, Porceddu S. Measuring head and neck lymphedema: The "ALOHA" trial. Head & Neck. (2016). 38(1):79-84. https://dx.doi.org/10.1002/hed.23853
22. Smith BG, Hutcheson KA, Little LG, Skoracki RJ, Rosenthal DI, Lai SY, et al. Lymphedema outcomes in patients with head and neck cancer. Otolaryngol Head Neck Surg. (2015). 152(2):284-91. https://dx.doi.org/10.1177/0194599814558402
23. Deng J, Murphy BA, Dietrich MS, Wells N, Wallston KA, Sinard RJ, et al. Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. Head Neck. (2013b). 35(7):1026-35. https://dx.doi.org/10.1002/hed.23084

24. Deng J, Ridner SH, Dietrich MS, Wells N, Wallston KA, Sinard RJ, et al. Prevalence of secondary lymphedema in patients with head and neck cancer. J Pain Symptom Manage. (2012). 43(2):244-52. https://dx.doi.org/10.1016/j.jpainsymman.2011.03.019
25. Micke O, Bruns F, Mucke R, Schafer U, Glatzel M, DeVries AF, et al. Selenium in the treatment of radiation-associated secondary lymphedema. Int J Rad Onc Bio Phy. (2003). 56(1):40-9.
26. Deng J, Ridner SH, Wells N, Dietrich MS, Murphy BA. Development and preliminary testing of head and neck cancer related external lymphedema and fibrosis assessment criteria. Eur J Oncol Nurs. (2015b). 19(1):75-80. https://dx.doi.org/10.1016/j.ejon.2014.07.006
27. Ayestaray B, Bekara F, Andreoletti JB. pi-shaped lymphaticovenular anastomosis for head and neck lymphedema: a preliminary study. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. (2013). 66(2):201-6. https://dx.doi.org/10.1016/j.bjps.2012.08.049
28. Brake MK, Jain L, Hart RD, Trites JR, Rigby M, Taylor SM. Liposuction for Submental Lymphedema Improves Appearance and Self-Perception in the Head and Neck Cancer Patient. Otolaryngol Head Neck Surg. (2014). 151(2):221-5. https://dx.doi.org/10.1177/0194599814529401
29. Deng J, Dietrich MS, Niermann KJ, Sinard RJ, Cmelak AJ, Ridner SH, et al. Refinement and Validation of the Head and Neck Lymphedema and Fibrosis Symptom Inventory. Int J Radiat Oncol Biol Phys. (2021). 109(3):747-55. Doi: 10.1016/j.ijrobp.2020.10.003

30. Deng J, Ridner SH, Murphy BA, Dietrich MS. Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer. Supportive Care in Cancer. (2012b). 20(8):1911-8. https://dx.doi.org/10.1007/s00520-011-1294-6
31. Deng J, Dietrich MS, Ridner SH, Fleischer AC, Wells N, Murphy BA. Preliminary evaluation of reliability and validity of head and neck external lymphedema and fibrosis assessment criteria. Eur J Oncol Nurs. (2016). 22:63-70. https://dx.doi.org/10.1016/j.ejon.2016.02.001
32. Ridner SH, Deng J, Doersam JK, Dietrich MS. Lymphedema Symptom Intensity and Distress Surveys-Truncal and Head and Neck, Version 2.0. Lymphat Res Biol. (2020). 19(3):240-248. Doi: 10.1089/lrb.2020.0071
33. Ridner SH, Dietrich MS, Deng J, Ettema SL, Murphy B. Advanced pneumatic compression for treatment of lymphedema of the head and neck: a randomized wait-list controlled trial. Support Care Cancer. (2021). 29(2):795-803. Doi: 10.1007/s00520-020-05540-8
34. Alamoudi U, Taylor B, MacKay C, Rigby MH, Hart R, Trites JRB, et al. Submental liposuction for the management of lymphedema following head and neck cancer treatment: a randomized controlled trial. J Otolaryngol Head Neck Surg. (2018). 47(1):22. https://dx.doi.org/10.1186/s40463-018-0263-1
35. Gutierrez C, Mayrovitz HN, Naqvi SHS, Karni RJ. Longitudinal effects of a novel advanced pneumatic compression device on patient-reported outcomes in the

management of cancer-related head and neck lymphedema: A preliminary report. Head Neck. (2020). 42(8):1791-9. Doi: 10.1002/hed.26110

36. Piso DU, Eckardt A, Liebermann A, Gutenbrunner C, Schafer P, Gehrke A. Early rehabilitation of head-neck edema after curative surgery for orofacial tumors. Am J Phys Med Rehabil. (2001). 80(4):261-9.
37. Doke KN, Bowman L, Shnayder Y, Shen X, TenNapel M, Thomas SM, et al. Quantitative clinical outcomes of therapy for head and neck lymphedema. Adv Radiat Oncol. (2018). 3(3):366-71. Doi: 10.1016/j.adro.2018.04.007
38. Gutierrez C, Karni RJ, Naqvi S, Aldrich MB, Zhu B, Morrow JR, et al. Head and Neck Lymphedema: Treatment Response to Single and Multiple Sessions of Advanced Pneumatic Compression Therapy. Otolaryngol Head Neck Surg. (2019). 160(4):622-6. https://dx.doi.org/
39. Mayrovitz HN, Ryan S, Hartman JM. Usability of advanced pneumatic compression to treat cancer-related head and neck lymphedema: A feasibility study. Head Neck. (2018). 40(1):137-43. https://dx.doi.org/10.1002/hed.24995
40. Tacani PM, Franceschini JP, Tacani RE, Machado AF, Montezello D, Goes JC, et al. Retrospective study of the physical therapy modalities applied in head and neck lymphedema treatment. Head Neck. (2016). 38(2):301-8. https://dx.doi.org/10.1002/hed.23899
41. Patterson JM, Hildreth A, Wilson JA. Measuring edema in irradiated head and neck cancer patients. Ann Otol Rhinol Laryngol. (2007). 116(8):559-64. Doi: 10.1177/000348940711600801

42. Starmer HM, Drinnan M, Bhabra M, Watson LJ, Patterson J. Development and reliability of the revised Patterson Edema Scale. Clin Otolaryngol. (2021). 46(4): 752-7. Doi: 10.1111/coa.13727
43. Akashi M, Teraoka S, Kakei Y, Kusumoto J, Hasegawa T, Minamikawa T, et al. Computed Tomographic Evaluation of Posttreatment Soft-Tissue Changes by Using a Lymphedema Scoring System in Patients with Oral Cancer. Lymphat. (2018). 16(2):147-53. Doi: https://dx.doi.org/10.1089/lrb.2016.0063
44. Aulino JM, Wulff-Burchfield EM, Dietrich MS, Ridner SH, Niermann KJ, Deng J, et al. Evaluation of CT Changes in the Head and Neck After Cancer Treatment: Development of a Measurement Tool. Lymphat. (2018). 16(1):69-74. https://dx.doi.org/10.1089/lrb.2017.0024
45. Turcotte MC, Herzberg EG, Balou M, Molfenter SM. Analysis of pharyngeal edema post-chemoradiation for head and neck cancer: Impact on swallow function. Laryngoscope Investig Otolaryngol. (2018). 3(5):377-83. Doi: 10.1002/lio2.203
46. Piso DU, Eckardt A, Liebermann A, Gehrke A. Reproducibility of sonographic soft-tissue measurement of the head and neck. Am J Phys Med Rehabil. (2002). 81(1):8-12. Doi: 10.1097/00002060-200201000-00003
47. Beelen LM, van Dishoeck AM, Tsangaris E, Coriddi M, Dayan JH, Pusic AL, et al. Patient-Reported Outcome Measures in Lymphedema: A Systematic Review and COSMIN Analysis. Ann Surg Oncol. (2021). 28(3):1656-68. Doi: 10.1245/s10434-020-09346-0

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4. Quality of life and its measurement: Understanding the patient perspective

4.1. Chapter introduction

The systematic review presented in Chapter 3 identified the nonexistence of a patient reported HRQoL instrument specific to HNL. Given the unique impact of HNL on factors that influence QoL such as appearance, communication, and eating, it appears appropriate and valuable to develop an HNL-specific HRQoL PROM. Studies have demonstrated a broad range of consequences of HNL including physical, emotional, functional, and social limitations (Deng et al., 2019; Deng, Murphy, et al., 2015; Jeans et al., 2019). In this chapter, I will explore the construct of HRQoL and emphasise the importance of qualitative methodology to understand the patient perspective. Additionally, I will discuss qualitative research methods.

4.2. Conceptualisation and models of health-related quality of life

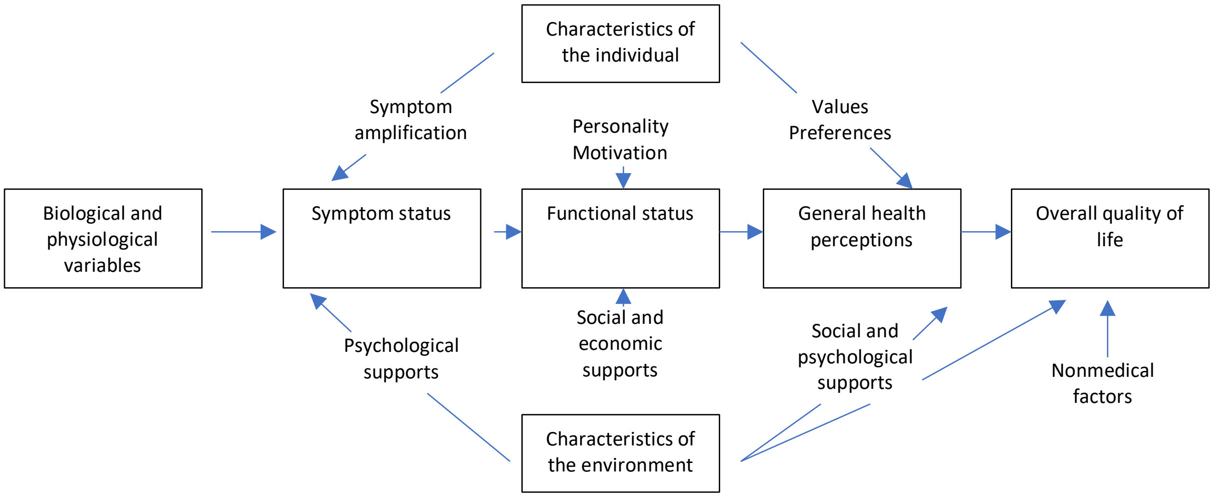
Health-related quality of life (HRQoL) reflects an individual's perceived well-being relative to their physical and emotional health. Several models of HRQoL have been proposed, particularly in respect to the measurement of HRQoL for different health conditions. According to a systematic review by Bakas et al. (2012), three models of HRQoL (Ferrans et al., 2006; WHO, 2001; Wilson & Cleary, 1995) are the most frequently used in health outcomes research. Wilson and Cleary (1995) provided an initial model of HRQoL which was later adapted into a second model by Ferrans and colleagues (2005). The third model was proposed by the World Health Organization (WHO) in 2001 and is known as the WHO International Classification of Function, Disability, and Health (WHO ICF).

4.2.1. Wilson and Cleary's model

Wilson and Cleary describe their model as a method to "distinguish among conceptually distinct measures of HRQ(o)L and to make explicit what we think are the dominant causal associations" (Wilson & Cleary, 1995, p. 60). They identify five interrelated concepts that may impact HRQoL: physiologic/biologic factors, symptoms, function, general health perceptions, and overall QoL. In this model (Figure 4-1), these factors interact with characteristics of the individual and their environment to impact

Figure 4-1 Wilson and Cleary's model of quality of life

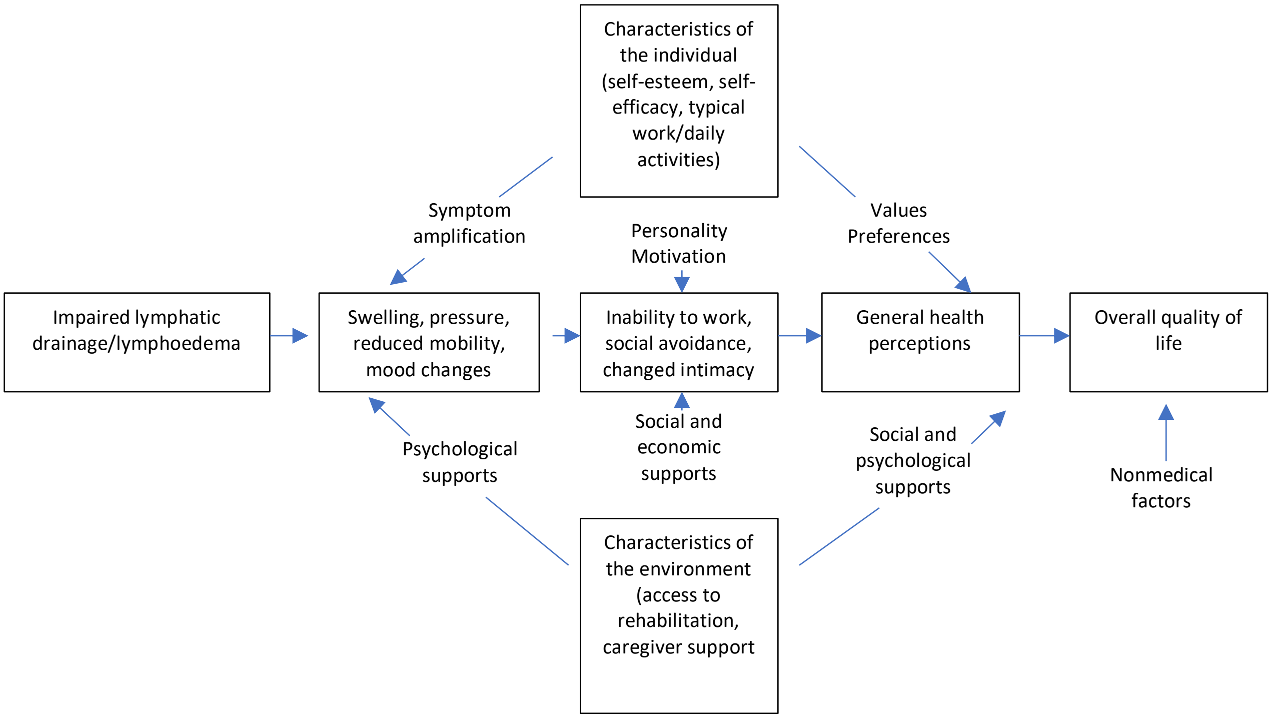
(Reprinted from Wilson & Cleary, 1995. With permission from the American Medical Association)



Biological and physiologic factors refer to the underlying structure and function of cells, organs, and organ systems. In reference to lymphoedema, this level would refer to injury to the lymphatic system leading to reduced lymphatic drainage. Symptoms are defined as “a patient’s perception of an abnormal physical, emotional, or cognitive state” (Wilson & Cleary, 1995, p. 61). Symptoms that might be attributed to lymphoedema include physical sensations like tightness, or emotional symptoms such as embarrassment about one’s physical appearance. Functioning refers to the individual’s ability to perform specific tasks. There are four domains of function which are most frequently measured by researchers applying this model: physical, social, role, and psychological function. Examples of functional disruptions attributed to lymphoedema are inability to work due to speech changes from lymphoedema and avoidance of social situations due to embarrassment regarding physical appearance. The fourth domain, general health perceptions, refers to an individual’s relative perception regarding their health status, which has been shown to correlate with seeking medical care (Connelly et al., 1989) and health outcomes (Idler & Kasl, 1991). An example of health perceptions regarding lymphoedema would be a patient who believes the presence of lymphoedema is indicative of a poor response to HNC treatment. Finally, overall QoL refers to an individual’s subjective view of their overall well-being or satisfaction with life. An individual with a higher overall QoL would be expected to also have a higher HRQoL regarding their lymphoedema. Wilson and Cleary acknowledge that as you move from left to right on this model, there is increasing complexity and interrelatedness related to the interaction of the physical being to the environment in which a patient functions.

What this means practically is that when striving to positively impact HRQoL, several influences must be considered, not merely physiologic contributors (Figure 4-2).

Figure 4-2 Head and Neck Lymphoedema Health-Related Quality of Life using Wilson and Cleary's model

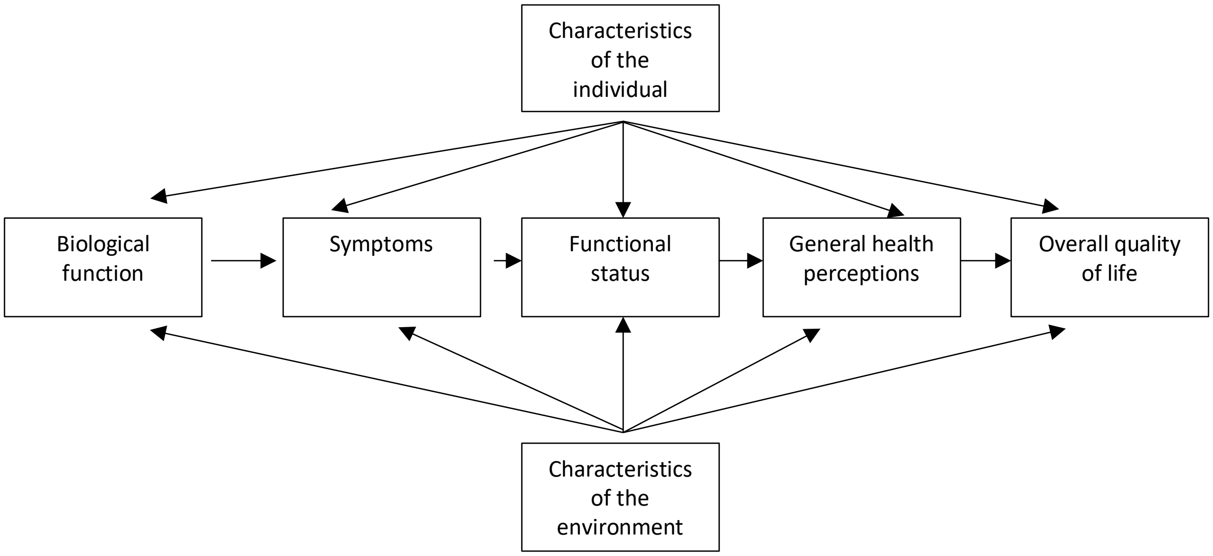


4.2.2. Ferrans' model

Ferrans et al. (2005) sought to revise the Wilson and Cleary model to provide further clarity regarding contributing factors that were not discussed in the manuscript of the original Wilson & Cleary model, and to clarify the relationships with primary contributors in the centre of the model (Figure 4-3). Individual and environmental characteristics were further characterised. Ferrans and colleagues provided a robust discussion of factors known to influence disease risk and outcomes such as genetic factors, age, marital status, and ethnicity. In addition to these personal characteristics, they also identified developmental status and psychological factors such as intrinsic/extrinsic motivation and affective response as features that may influence health outcomes and HRQoL. In respect to environmental characteristics, they classified these as either social or physical. Social characteristics include interpersonal and social influences whilst physical characteristics refer more to physical locations such as the home, neighborhood, and workplace. The revised model added arrows between individual and environmental factors and biological factors to acknowledge that both may influence physiology. They also opted to delete the “nonmedical factors” box as these factors could be accounted for under either individual or environmental characteristics. Finally, they opted to remove examples of individual and environmental characteristics in the figure as these were more completely described in the manuscript.

Figure 4-3 Ferrans' revision of Wilson & Cleary's model of HRQoL

(Reprinted from Journal of Nursing Scholarship, Volume 37, Issue 4. Ferrans et al., Conceptual model of health-related quality of life, p. 338. 2005. With permission from John Wiley and Sons.)

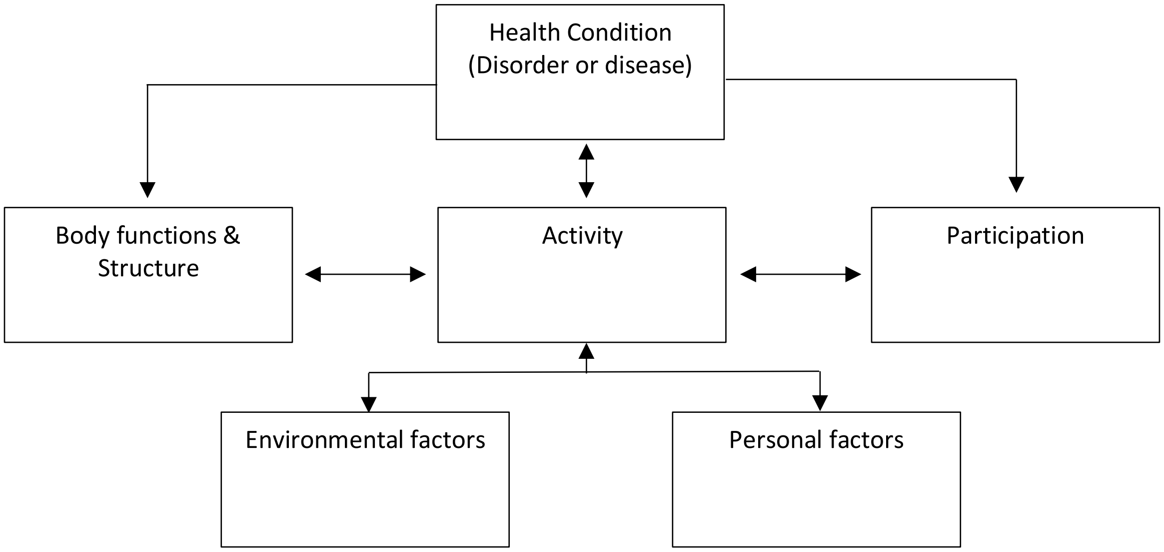


4.2.3. WHO International Classification of Function, Disability, and Health model

The WHO ICF is a "classification of health and health-related domains… that help us to describe changes in a body function and structure, what a person with a health condition can do in a standard environment (their level of capacity), as well as what they actually do in their usual environment (their level of performance)" (WHO 2001, p. 2). It is an evolution from earlier WHO publications which focused more on the consequences of disease (WHO, 1980). The 2001 ICF focused more on health impact and perceptions of health and well-being (WHO, 2001). The ICF was developed to provide a tool to be used in policy making and planning at a global level. It sought to provide a common nomenclature regarding health and health-related functioning.

The ICF is based upon the biopsychosocial model of disability which considers the physical, personal, and social contributors to disability. It acknowledges that disability and function are the result of the bidirectional interaction between the health condition, the individual, and contextual factors (Figure 4-4). Thus, disability occurs when a disease or condition creates disturbance of body structures and their function, activities, and/or life participation in the context of the physical and psychosocial environment in which the individual lives and is influenced by personal factors. An example of potential disability related to the ***health condition*** HNL using this framework includes ***impairment*** in respect to reduced neck mobility that may lead to ***activity limitation*** of difficulty turning the head to check blind spots when driving which may lead to ***participation restriction*** of not attending social gatherings due to an inability to drive safely. Thus, this model focuses predominantly on the functional impact of a disease but not as much on the individual's perception of those functional changes.

Figure 4-4 The WHO ICF (WHO, 2001)



4.2.4. Considerations when applying health-related quality of life models

Irrespective of which HRQoL model is being used, when considering function, disability, and rehabilitation, it is critical to acknowledge that the diagnosis of a specific health condition is not predictive of how an individual may be impacted by that condition (Ashley et al., 2015; Hulbert-Williams et al., 2012; Wakefield, 2009). Contextual factors may result in differential risk for disability across individuals (WHO, 2012). In a rehabilitation setting, understanding an individual's HRQoL is critical for identifying the impact of a condition on functioning and life participation to appropriately provide interventions to mitigate the negative impacts of the condition on functioning and well-being. Such interventions may be aimed at improving the functional capacity of the individual or modifying the social and physical environment in which the individual needs to function. Returning to the example of HNL related QoL using the WHO model, in an individual whose lymphoedema has resulted in reduced social participation, interventions may target either the physical limitations of neck mobility, challenges with driving, or finding new ways for the individual to engage in social activities. The three models of HRQoL reviewed herein highlight the importance of considering not only the individual but also the environments in which they live, work, and socialise.

4.3. Lymphoedema and quality of life

There has been substantial research into HRQoL in individuals with other types of lymphoedema that may be informative for researchers interested in HNL. For example, many studies have shown that women with lymphoedema following breast cancer treatment experience numerous impacts on quality of life including diminished function in the impacted upper limb, limitations in what types of clothing they can wear, and embarrassment with their appearance (Hull, 2000; Stamatakos et al., 2011; Taghian, et al., 2014). Similarly, individuals with lower limb lymphoedema may have issues with mobility, performing daily tasks, and intimate relationships (Carter et al., 2021; Cemal et al., 2013; Finnane et al., 2011). Although there may be some similarities in HRQoL concerns across lymphedema subtypes (e.g. embarrassment about appearance), the distinct challenges of oedema in the head and neck region (e.g. breathing, speaking, and eating) require special consideration. HRQoL measurement instruments for lymphoedema such as the Lymphedema Quality of Life Inventory (LyQLI) focus on broad issues across the domains of physical, psychosocial, and practical concerns, but do not account for concerns common to those with HNL such as difficulties related to breathing, eating, speaking, sight, and hearing.

4.3.1. Health-related quality of life in individuals with head and neck lymphoedema

As mentioned previously, HNL may have numerous and varied impacts including physical challenges, activity limitations, and restricted participation in meaningful life activities (see section 4-3-2). Early investigations of the relationship between HNL and QoL (Bruns et al., 2004; Micke et al., 2003) demonstrated a relationship between severity of HNL and overall QoL. These studies provided important insight into the relationship between HNL and overall QoL, however, in both investigations, a non-validated visual analogue scale (VAS) was utilised to quantify QoL. Although this provided general information about QoL, it lacked the type of specificity that would be important clinically to identify intervention needs. Additionally, it was not clearly indicated in either manuscript whether the QoL rating was provided by the patient or the healthcare provider. This is problematic in that clinician and patient ratings of QoL are consistently shown to be poorly correlated (Coran et al., 2013; Herman et al., 2013; Wilkie et al., 2019; Wilson et al., 2000). Though these early studies provided the first evidence of a relationship between HNL and QoL, they lacked specificity for understanding if specific factors were particularly influential to HRQoL. To establish the relationship between oedema severity and HRQoL and its contributors, Deng et al.

(2010) called for the use of validated measures to demonstrate this relationship in future studies.

4.3.2. Symptom burden in head and neck lymphoedema

Subsequent studies have explored issues around symptom burden associated with HNL. Deng, Murphy, et al. (2013) performed a cross-sectional analysis of individuals more than 3 months following treatment for HNC. In this sample of 103 patients, they found evidence of external lymphoedema in 46% of participants and internal lymphoedema in 68% of those undergoing endoscopic evaluations. Using the Vanderbilt Head and Neck Symptom Survey (VHNSS), they demonstrated that those diagnosed with lymphoedema had greater issues with swallowing, nutrition, dry mouth, and voice than those without HNL. Further, those individuals with lymphoedema were found to have higher degrees of distress regarding their physical appearance using the Body Image Scale. This finding was particularly salient for those with external lymphoedema. The Functional Assessment of Cancer Therapy- Head & Neck (FACT-HN) was used to measure overall HRQoL. They found a significant association between lymphoedema severity and overall HRQoL, with greatest associations found between lymphoedema severity and the 'functional' and 'head and neck' subscales of the FACT-HN. These findings were among the first to demonstrate a correlation between HNL and increased symptom burden, functional restrictions, and worsened HRQoL.

4.3.3. Qualitative research in head and neck lymphoedema

A qualitative evidence synthesis does not currently exist regarding HNL and HRQoL. HRQoL is frequently explored through qualitative research approaches. McGarvey and colleagues (2014) completed a qualitative study in Australia with patients with HNL as well as medical providers to better understand the impacts of HNL. They interviewed ten patients diagnosed with HNL and ten medical providers including two radiation oncologists, two surgeons, two physiotherapists, a dietician, a nurse, a care coordinator, and a speech and language therapist (SLT). In general, the perceptions expressed by patients and clinicians were quite similar, however clinicians were more likely to minimize the impact of HNL on patients. From the patient interviews, the authors generated two primary themes regarding HNL impact: physical effects and psychological/social effects. Altered appearance and body image distress were themes common to most participants. This was also identified by medical providers who felt that the primary impact of HNL on patients is regarding appearance and self-image. Similar to McGarvey; Deng, Murphy, et al. (2013) found distress related to body image. These results highlighted one difference between HNL and limb lymphoedema, its visibility and difficulty obscuring the oedema from others. While this study provides some insight into the impact of HNL, a major concern regarding this study is the brevity of the interviews which ranged from 3-30 minutes with a mean duration of 8 minutes. This raises questions regarding the comprehensiveness of these interviews and their ability to reach appropriate levels of data saturation/information power. Additionally, the majority of participants were ~1 year post HNC treatment, therefore may not have been actively dealing with HNL leading to some recall bias. Furthermore, the timing of when the participants underwent HNL treatment is not reported nor is the severity level of their oedema. Thus, there are significant limitations to the information provided by this study.

Deng et al. (2013) identified dysphagia, dysphonia, and speech differences in patients with HNL. As a result, Jeans and colleagues (2018) conducted semi-structured interviews with twelve individuals with HNL to further explore the functional consequences of HNL, focusing on swallowing, voice, and speech. Most participants (10/12) felt they had changes to their voice following cancer treatment; however, they were unable to confidently attribute these changes to lymphoedema. Thus, the focus of the analysis was the impact of HNL on speech and swallowing. Four primary themes were developed from these interviews: “it feels tight”, “it changes throughout the day”, “it requires daily self-monitoring and management” and “it affects me in other ways.” Participants felt there was a direct relationship between the sensory changes associated with HNL and difficulties swallowing and speaking. Despite the focus of interviews on speech, voice, and swallowing, most participants mentioned other impacts of HNL. For example, most participants expressed that HNL had an impact on emotional well-being, however due to the focused intent of this investigation, this theme was not thoroughly explored.

Nixon and colleagues (2018) used a mixed methods design to explore distress and HRQoL in patients with HNL. Distress was measured using the Distress Thermometer and HRQoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: Head and Neck 43 (EORTC-QLQ-H&N43). Additionally, they conducted semi-structured interviews with participants following a course of HNL treatment (n=10). They identified six themes from the qualitative interviews including: psychosocial impacts, physical experiences, experiences of receiving treatment, day-to-day distress, and adjusting to a "new normal". All participants in their study reported distress and impaired psychosocial functioning related to their HNL at baseline, a finding that has not been previously reported. A unique aspect to this study was the comparison of results of a validated HRQoL instrument and the qualitative interviews. Interestingly, they found discrepancies between scores on the EORTC-QLQ-H&N43 and patient reports during qualitative interviews. For example, whilst scores for body image concerns were low, participants expressed significant appearance related concerns during qualitative interviews (e.g. avoidance of looking in the mirror), suggesting that general HRQoL instruments lack sensitivity to the subtle issues associated with HNL.

Based on research to date, there appears to be a relationship between HNL and HRQoL. Many of the impacts of HNL appear to be unique due to the body systems impacted in the head and neck region. The lack of concordance between existing general HNC HRQoL instruments and the lived experience of those with HNL supports the need for HRQoL measurement tools that specifically consider the unique impacts of this condition. Further, it is critical to have a method to understand the specific impacts of HNL on an individual to tailor patient-centered interventions.

4.4. Research paradigms

The methods chosen for any research project may be influenced by the research question itself as well as the underlying philosophies of the investigator. Broom & Willis (2007) define a research paradigm as, “an overarching philosophical or ideological stance, a system of beliefs about the nature of the world, and ultimately, when applied in the research setting, the assumptive base from which we go about producing knowledge” (p. 17). Research paradigms reflect how a researcher views the world and influence the research methods employed as well as the interpretation of their findings.

The paradigm selected for a particular research project is largely driven by the motivations behind engaging in the research (Brown & Duenas, 2020). Whilst there are many different research paradigms, in medical research, four paradigms are frequently employed (Brown & Duenas, 2020; Bunness & Kelly, 2010; Weaver & Olson, 2006). These include positivist, post-positivist, constructionist, and critical theory approaches. Those from a positivist philosophy believe there are truths that can be known which are measurable and constant. Post-positivists believe that whilst there are fixed truths, there is some degree of variability or error in human measurement which may lead to imperfection in characterising these “truths”. Thus, post-positivists are more likely to consider reality as composed of “probable truths” rather than “definite truths.” Constructivists believe that individuals construct their truth and therefore that truth is not fixed and cannot be quantified. Critical theory also asserts that truth is constructed, but also that truth is heavily impacted by societal and power variables.

Brown & Duenas (2020) provide a helpful framework for thinking about defining paradigms behind a particular body of research. Historically, ontology, epistemology, and methodology have been considered the bedrocks of paradigm building (Guba & Lincoln, 1994). Based on writings of Heron & Reason (1997), Brown and Duenas propose the addition of axiology as the first consideration for paradigm building. They provide an adaptation of Grix's paradigmatic building blocks (2002) where the building blocks of a paradigm include axiology, ontology, epistemology, methodology, methods, and sources (Figure 4-5). Table 4-1 demonstrates how different research paradigms think about these core building blocks.

Figure 4-5 Adaptation of Brown & Duenas paradigmatic building blocks (2020)

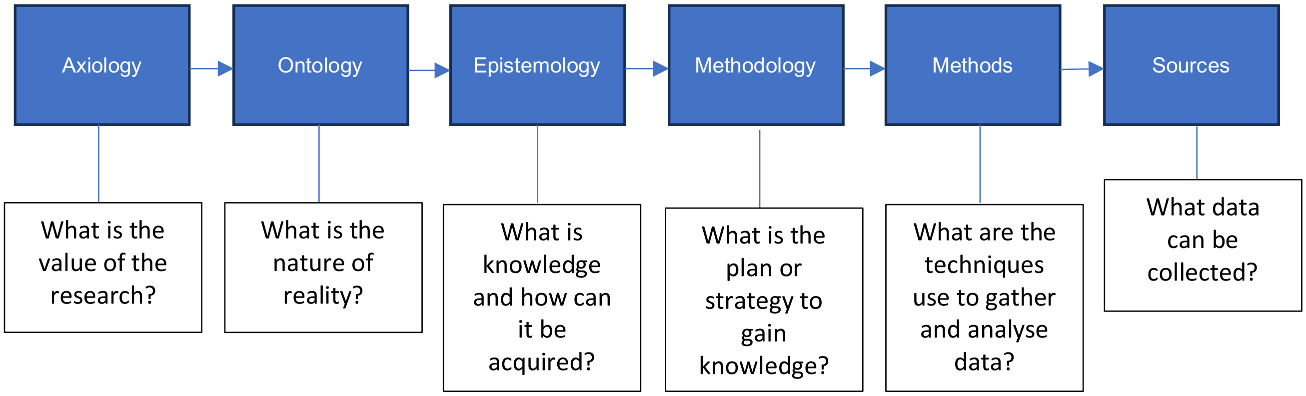


Table 4-1 Research paradigms

(adapted from Bunniss & Kelly, 2010, with permission from John Wiley and Sons Publishing)

	Positivism	Post-positivism	Constructionism	Critical theorism
Axiology	Goal is to discover and describe truth.	Goal is to discover and describe probable truth.	Goal is to understand human nature.	Goal is to identify injustices and to empower individuals to create systemic change.
Ontology	Reality is static and fixed.	Reality is static and fixed, but science involves error, so truth is not perfect.	Reality is subjective and not fixed.	Reality and truth are influenced by social, political, cultural, and other values.
Epistemology	Knowledge can provide accurate descriptions of the world when reliable and valid tools are used.	Knowledge is not fully accessible because human interaction with research leads to error. Truth is probable rather than defined.	Knowledge is subjective. There may be many versions of truth depending on individual interpretations.	Knowledge is influenced by power and societal impacts. Truth fluctuates according to current power structures and among different groups.
Methodology	Uses scientific method to describe and predict truth. Theory is deductive.	Uses empirical testing to refute hypotheses. Theory is deductive.	Uses qualitative methods to understand meaning. Theory is inductive.	Uses qualitative methods and frequently focuses on inclusion of diverse and under-represented views. Theory is inductive.
Methods	Quantitative methods and statistical analysis. (e.g. validated measures)	More frequently uses quantitative methods. (e.g. structured questionnaires)	Qualitative methods (e.g. semi-structured interviews)	More frequently uses qualitative methods. (e.g. focus groups)

4.4.1. Axiology

Axiology is concerned with the value and ethics of research (Varpio & MacLeod, 2020). It asks, “what is the value of a particular inquiry” and then requires the investigator to consider any ethical issues that may impact why the research is being performed (e.g. funding sources or other conflicts of interest). For this thesis, the overarching motivations for this work were my experiences and frustrations as a clinician and clinical researcher trying to capture meaningful outcomes in patients with HNL. Although tape measures and other quantitative measures may show changes in the severity of oedema, they do not seem to consistently account for the patient's experience of lymphoedema and treatment. Hence, the potential *value* of this inquiry was to understand better what patients with HNL experience, to drive future research into capturing the patient experience and to develop patient-centered interventions.

4.4.2. Ontology

Ontologic assumptions involve the nature of reality. Ontologic assumptions are commonly dichotomised into realist or relativist philosophies (Braun & Clarke, 2013). A researcher from the realist philosophy assumes that reality is concrete and constant. Thus, "truth" can be measured in an objective manner. Quantitative methods are most employed by those with a realist philosophy. In contrast, researchers from the relativist philosophy believe that reality is constructed through multiple influences and is not fixed. Researchers from the relativist philosophy are more interested in exploring the lived experiences that may influence an individual's constructed "meaning". In this philosophy, "truth" cannot be objectively measured (Bryman, 2001). Qualitative research methods are generally utilised by those with a relativist philosophy.

Traditional realist approaches to researching HNL have been frustrating to me as a clinical researcher. So much of the patient experience of HNL appears to be subjective in nature – some patients with very little oedema are very bothered by it whilst others with very substantial oedema give it little thought. Thus, in thinking about the reality in which I think about HNL, I am approaching this research from a relativist perspective. I do not believe there is one fixed reality regarding the impact of HNL on HRQoL, and thus the individual's constructed reality needs to be considered. One might argue as well that a critical theory approach may be applicable to this work. Certainly, how society defines beauty, values appearance, and criticises obesity may construct a reality where HNL is more distressing. This consideration of cultural influences and context is why I opted to interview individuals from both the US and the UK. Although there may be many similarities between these cultures, there are also likely some differences in values and context that might influence how individuals think about their reality with HNL. But as the intent of this work is to develop a patient-centric tool, I chose to focus more on the patient perspective rather than the sociopolitical forces that may also influence those patient perceptions, thus remaining grounded in a HRQoL perspective rather than an overarching QoL perspective.

4.4.3. Epistemology

Epistemology refers to the nature of knowledge and how we obtain knowledge (Audi, 2011). Clearly, one's ontologic perspective will influence epistemology. For example, for those with a positivist approach where reality is fixed, the assumption is that that reality can be directly measured. In contrast, those from a constructionist perspective where reality is “in the eyes of the beholder”, knowledge is understood to be subjective in nature and not necessarily reflective of a universal truth.

Given that I approach this work from a constructionist perspective, the goal of understanding the patient’s perception assumes that I will need to include a variety of individuals and their perceptions to try to capture the most important aspects that specific individuals may report. The most appropriate way to obtain that knowledge is directly from a variety of individuals with firsthand experience of HNL. With a research goal such as the development of a PROM, open-minded exploration of the lived experience of those with the condition in question is critical to developing a rich understanding of the patient perspective. This is supported by numerous publications which cite patient involvement as of paramount importance in developing a valid PROM (Carlton et al., 2020; Comins et al., 2021; Farnik & Pierzchala, 2012; Weldring & Smith, 2013; Wiering et al., 2017). So, in this instance, my epistemological assumption is that aspects of HRQoL related to HNL can be learned and are most appropriately learned by specifically discussing them with individuals with HNL.

4.4.4. Methodology and Methods

Though the terms methodology and methods are sometimes used interchangeably, there are specific differences between the two terms. Methodology refers to the comprehensive plan to acquire knowledge, whilst methods refer to the specific techniques used to collect and analyse data (Braun & Clarke, 2013). For example, qualitative research may be considered a methodology, where semi-structured interviews and three-step interviews might be the specific methods employed. As my goal was to understand the patient perspective, with the intention of developing an HNL specific HRQoL measure, it was important to employ the methodology of qualitative research to gain a richer understanding of the patient experience. The specific methods such as semi-structured interviews will be discussed in greater detail in section 4-6.

4.5. Qualitative research

To understand HRQoL concerns for any condition, it is critical to consider the lived experiences of individuals impacted by the condition. Qualitative research is a valuable tool for systematically assessing the perspective of individuals within their social context (Patton, 1990). Qualitative research may be divided into two different approaches: experiential or critical qualitative research (Braun & Clarke, 2013). Experiential approaches prioritise the participant's experiences and interpretations of events. It seeks to understand how an individual experiences their world through their words. In contrast, critical approaches allow the researcher to look at the qualitative data in a broader context. It is concerned with how language creates meaning around a concept. When a critical approach is taken to qualitative research, the language used by participants is seen as constructing reality, not reflecting it. I selected the experiential approach for this research to be true to the voice and experience of the participants.

4.6. Methods of qualitative research

Several different methods may be employed in qualitative research including, but not limited to interviews, focus groups, surveys, diaries, and ethnographic observations. The types of methods employed by a qualitative researcher will depend upon the research question and theoretical approach. For this research, I chose a qualitative interview approach as I considered it to be most likely to yield comprehensive personal accountings of living with HNL.

4.6.1. Qualitative interviews

Qualitative interviews are particularly beneficial for studying that which cannot be viewed externally – feelings, emotions, perceptions, and intentions (Patton, 1990). Qualitative interviews allow the researcher to better understand the perspectives of individuals or groups. It makes explicit what is usually unsaid or unknown. According to Patton (1990), “the quality of the information obtained during an interview is largely dependent on the interviewer.” (p. 279). Thus, the researcher engaged in qualitative interviews must have a clear intention guiding the research as well as the skills to elicit and interpret meaning from interviews.

4.6.2. Sampling for qualitative research

One critical aspect of qualitative research is determining the appropriate sample for the research question at hand. Emmel (2013) describes three primary strategies for theoretic-based sampling in qualitative research: theoretical, purposive, and purposeful sampling. Theoretical sampling is selected when the goal of the research is to develop theory over time. Decisions are made about who to interview next based on the development of theory – in other words, this is an approach used with emergent theoretical approaches. In contrast, purposive sampling is described as driven by extant theory about the construct to be studied. This approach allows for flexibility and calls for revisiting “intellectual work” over the course of the study to influence future sampling decisions. In contrast to theoretical and purposive sampling, decisions are generally made a priori in purposeful sampling. Here the researcher determines what types of cases are most likely to yield “information rich data” in advance of data collection, again influenced by extant information and theories.

4.6.3. Intentional sampling strategies

Participant sampling in qualitative research is typically intentional, meaning that individuals are selected to participate as they are believed to have personal and in-depth knowledge of the construct of interest, so called “information-rich subjects” (Patton, 1990). Although demographic or other participant variables are used in quantitative research to ensure the sample is representative and can be generalised to the population at large, in qualitative methods, participants with different characteristics are sought out as they are believed to potentially influence the participant’s perspective on the construct of interest. Thus, participants from different groups are believed to bring unique information to the research. Qualitative research does not aim to generate information that can be universally representative – the goal instead is to gain a better understanding of the construct of interest in a designated sample. Patton (1990) described fifteen specific types of purposive sampling that are commonly employed in qualitative research (Table 4-2).

Table 4-2 Purposeful sampling strategies

(Adapted from Patton 1990, with permission from Sage Publishing)

Type of sampling	Goal
(1) Extreme/deviant case sampling	To learn from highly unusual cases.
(2) Intensity sampling	To identify information-rich cases that are on one end of the spectrum or another, but not extreme cases.
(3) Maximum variability sampling	To identify different variations that may exist due to differing exposures. May help to identify commonalities among a diverse population.
(4) Homogenous sampling	To focus in on a specific trait or construct.
(5) Typical case sampling	To illustrate the construct of interest in an average sample.
(6) Stratified purposeful sampling	To identify characteristics of subgroups of a population. May facilitate comparisons.
(7) Critical case sampling	To generalise information to other cases by selecting a case that should represent many others.
(8) Snowball sampling	To identify appropriate participants through other informants.
(9) Criterion sampling	To select all cases that meet a particular criterion. May contribute to quality assurance.
(10) Theory based sampling	To identify examples of a theoretical construct of interest.
(11) Confirming and disconfirming cases	To test hypotheses and expand on initial analyses.
(12) Opportunistic sampling	To take advantage of new leads identified during data collection.
(13) Random purposeful sampling	If the population of the construct is too large to sample, this helps to add to credibility of sample.
(14) Sampling politically important cases	To sample from politically extreme viewpoints.
(15) Convenience sampling	Used for convenience only – no longer recommended as a valid sampling strategy.
(16) Combination sampling	To be used when multiple sampling strategies may yield ideal participant sample.

4.7. Sampling in this research

For the question at hand about how HNL impacts HRQoL, it was important to recruit a broad sample of participants using purposive sampling. Based upon my clinical experience, I had some hypotheses about how HNL might impact individuals differently. I had seen that my younger patients appeared to have a higher degree of distress related to their HNL than many of my older patients. Similarly, there seemed to be different concerns expressed by those in the workforce and those not in the workforce. Sex also seemed to be associated with different concerns among my patients. Maximum variation sampling allowed me to identify participants possessing certain characteristics that I believed might influence HNL-related HRQoL. Characteristics such as age, sex, race, and socioeconomic status were purposively sampled. I also wanted to include participants with varying severity of HNL and different sites of HNC as both may impact the nature of the oedema and its impacts. Additionally, I opted to include participants from two countries (UK and US) which have different health care systems as well as different cultural values to gain insight about how HNL might be experienced differently in these different countries.

Given that caregivers and clinical professionals may have different perspectives on the impact of HNL, it is reasonable to also consider inclusion of their perspectives in this qualitative work. Because the primary aim of this phase of the thesis was to explore the *patient* perspective specifically, I decided not to include caregivers or professionals at this phase of research. However, the important perspectives of clinicians were integrated into later stages of this thesis which will be described in Chapters 5 and 7.

Though caregivers were not included in this thesis, a prior qualitative study I completed with caregivers of individuals with HNL provided me with some insight into their perspective of the condition and its impact on their loved ones (Starmer et al., 2022).

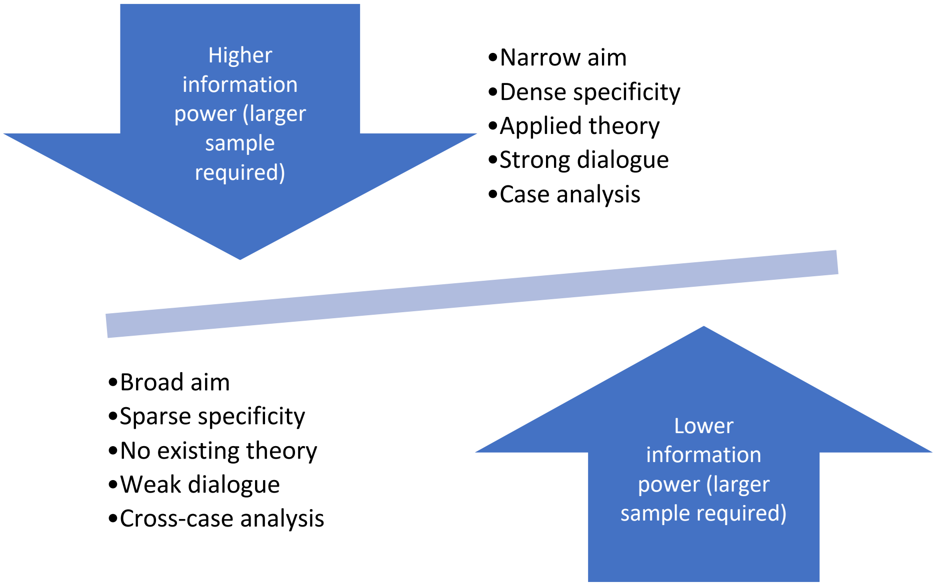
4.8. Determining sample size

Determining sample size for qualitative studies is quite different from quantitative research. As the intent of qualitative work is to explore experiences rather than uncover a universal truth, smaller sample sizes are generally utilised (Patton, 1990). Emmel (2013) lists two "rules" commonly applied to sampling in quantitative work; (1) "defining a population from which a sample will be drawn and of which the sample will be representative" and (2) "ensuring that every person or thing from this predefined population has the chance of inclusion that is greater than zero and can be measured" (p. 1). These rules are reflective of the differences in ontological perspectives underlying quantitative research methodologies.

The concept of data saturation is instead used in qualitative research to determine when enough data has been collected. Data saturation refers to the point in which additional data collected fails to generate any new or additional information (Hennick et al., 2017; Morse, 1995). Saturation indicates that a sample has adequately represented the concept that is being investigated and reflects content validity (Francis et al., 2010). Despite the importance of data saturation in qualitative research, it is uncommon for qualitative studies to disclose specifically what criteria are utilised to determine saturation (Carlsen & Glenton, 2011; Vasileiou et al., 2018).

Malterud (2016) describes “information power” as another principle to be considered when determining sample size for qualitative research studies. Information power suggests that the more information a particular sample holds about the construct of interest, the fewer participants will be required to meet the aims of the study. They propose five considerations that may influence information power: the aim of the study, the specificity of the sample, use of established theory, the quality of the dialogue, and the analysis strategy. Studies with a narrower aim will generally require a smaller sample size to reach their intended goal. Similarly, a smaller “n” would be needed when the available sample has specific, deep expertise in the construct of interest. In respect to established theory, studies based on existing theory will generally require a smaller sample than those needing to establish and build theory based on the qualitative work. The quality of the dialogue refers to the shared interaction between the researcher and the participant. When these interactions yield rich and clear communications, fewer interviews are generally required to meet the study aims. Here the skill of the interviewer in building rapport is critical. Finally, the strategy selected for data analysis can impact the required sample size. In-depth analysis of recorded narratives may require fewer participants than a study looking to use cross-case analysis. Figure 4-6 provides an adapted representation of this “information power” framework.

Figure 4-6 Adaptation of Malterud's "Information Power" model (Malterud, 2016)



Some researchers have utilised quantitative methods to try to numerically define data saturation. Hennick & Kaiser (2022) performed a systematic review of studies using empirical methods to determine saturation in qualitative investigations. Code frequency counts were most employed to determine saturation. Six studies reported using statistical modeling to determine saturation. Across the different quantitative approaches to determining saturation, the number of interviews required ranged from 5-24 with a mean of 12-13 interviews across methods. Thus, the researchers concluded that, a sample size in this range is likely to yield a good representation for most studies. Of course, who is included in that sample has the potential to significantly impact the outcomes of the investigation. For example, if only patients with very mild lymphoedema were included in a qualitative study of the impact of HNL on HRQoL, an investigator might incorrectly deduce that there is limited potential impact of HNL on HRQoL. Thus, in addition to considering data saturation and information power, the researcher must be thoughtful about including those with a potential wide variety of experiences and opinions about a construct.

4.9. Conducting qualitative interviews

Although there are several different strategies that can be employed in qualitative research, I selected individual interviews as the most appropriate strategy to address my question of how HNL impacts individuals. Whilst focus groups may have also yielded valuable information, I wanted to provide a format where more reticent patients would feel comfortable discussing issues that might be sensitive, like physical appearance, mood impacts, and intimacy. Furthermore, the one on one format appeared more appropriate given the potential for speech and voice difficulties in a population of patients treated for HNC that might contribute to lack of comfort speaking in a group setting.

Qualitative interviews can provide rich, detailed information if performed well and if driven by a well-defined research question. In contrast to quantitative research where the research question is fixed over the course of the study, the research question in qualitative research may evolve over time (Bhangu et al., 2023). Based on the initial research question, the investigator develops an initial interview guide to explore aspects of the construct of interest. Over time, and in response to participant interviews, the interview guide may be adapted to explore other concepts that are raised during the interviews (Braun & Clarke, 2013). Thus, the specific questions asked may also evolve over time. For this study, the overarching research question was: *In what ways does head and neck lymphoedema impact quality of life?* Based on early interviews, some concepts emerged that appeared worthwhile for additional interrogation; thus, I adapted the interview guide accordingly (see Chapter 6).

There are three primary types of interviews used in qualitative research: structured, semi-structured, and unstructured (Braun & Clarke, 2013). Structured interviews include a finite set of questions and response options which are pre-determined by the researcher. In contrast, semi-structured interviews involve a set of initial questions to be posed by the researcher, but with the flexibility for the participant to raise other questions or concepts during the interview. The interviewer conducting semi-structured interviews may vary the wording and order of questions to naturally flow with the interviewee's responses. Thus, the semi-structured interview is conversational, but also benefits from having some predefined questions and concepts that are always addressed during the interview. During unstructured interviews, a researcher may have a list of overarching themes of interest, however the interview is predominantly lead by the participant and what they are interested in discussing within the context of the research question. In qualitative research, the semi-structured interview is most employed (Braun & Clarke, 2013) as it allows the researcher to address areas of interest whilst remaining flexible to the insights of the research participant.

4.9.1. The interview guide

The interview guide should be constructed prior to initiating interviews but may be updated over the course of subsequent interviews to address themes that arise (Charmaz, 2002). Early interview questions should be designed to establish rapport between the interviewer and interviewee. It is good practice to transition from more general questions to more specific and probing questions over the course of the interview. The interview guide should loosely be organised by related concepts or themes. Questions should be worded in a way to maintain rapport and optimise the potential of participants sharing freely. Braun & Clarke (2013) offer the following suggestions for crafting effective interview questions.

- Do ask open ended questions (e.g., tell me more about when you first noticed the swelling.)
- Don’t ask leading questions (e.g., some people think lymphoedema means their doctor did something wrong. What about you?)
- Don’t ask questions asking about multiple things (e.g., When you first noticed the swelling, how did you feel? How do you think that impacted your actions?)
- Don’t ask long, complicated questions and those using double negatives (e.g., So you don’t not like it?)
- Do ask clear and precise questions, avoiding ambiguous terms (e.g., When I say sex, I mean sex assigned at birth. How does your sex influence how you think about your oedema?)

- Do ask linguistically appropriate questions for interview participants – avoid jargon or over-simplified language (e.g., tell me about your cancer journey in your own words)
- Don’t ask questions that assume something about your participants (e.g., You must be really embarrassed about your lymphoedema, tell me more about that.)
- Do ask empathetic, non-threatening questions (e.g., That must have been really challenging. Tell me more about how you dealt with that)

4.9.2. Effective interviewing strategies

There are several attributes that will contribute to the success of the qualitative researcher. As previously mentioned, the interviewer must prepare in advance, formulating a research question and interview guide that will allow the interviewer to probe constructs of interest. Prior to initial interviews, there is some benefit to doing a practice or pilot interview to test out the interview guide and to obtain some feedback regarding interview style and technique (Kallio et al., 2016). I was able to complete a pilot interview with a patient who had been treated for HNL in my clinic and he provided valuable feedback about question clarity and interview flow.

Building rapport with the participant is crucial to obtaining abundant and in-depth data (Braun & Clarke, 2013; Charmaz, 2014; Patton, 1990). It is important to recognise there may be power differentials between an interviewer and their interviewee. This is particularly true when there is a pre-existing relationship between the two parties. Particularly in the context of a healthcare provider interviewing a patient, significant care must be taken to minimise the potential for coercion or perceived coercion due to existing societal power differentials (Beisecker, 1990). The interviewer should utilise open ended questions that allow participants to expand on their statements. Additionally, the interviewer should employ active listening to respond to and adapt the interview based on the responses provided by the participant. Ideally the interview will be audio recorded to allow for direct transcription and to allow the interviewer to be more engaged in the interaction, rather than taking copious field notes. At the conclusion of the planned interview, it is important to give the interview participant the opportunity to add any other information they feel is relevant and important.

4.9.3 The dual role of researcher and clinician

Clinicians participating in research bring added value to the work such as consideration of clinical relevance, first-hand expertise in the care of patients with a particular condition, and access to participants needed for a given research project. These benefits, however, must be balanced with the potential negative impacts of their participation. Concerns about clinician participation in research may include issues such as conflicting ethical responsibilities, competing obligations, and lack of role clarity (Hay-Smith et al., 2016). Considerable reflexivity on the part of the researcher is required to balance these issues that may compromise transparency and trustworthiness of the research. Further, care must be taken to minimise the potential sense of coercion or power differential between the interviewer and participant.

Hay-Smith described “over-identification with the clinical self” as one of the challenges a researcher may face. The participant in the research may similarly find it challenging to distinguish between the interviewer’s role as a clinician and that of a researcher. This may be particularly salient when the researcher/interviewer and the participant have an existing or prior clinical relationship. This difficulty in maintaining distinctive role boundaries must be considered and intentionally guarded against. This can occur by design methodologically (Hunt et al., 2011). For example, during my research, all interviews were performed virtually which allowed for a degree of separation from the clinical environment. Additionally, during interviews I wore casual-professional clothing rather than the scrubs and lab coat that my patients are used to seeing me in in the clinical setting. Finally, the background I used during interviews was a non-clinical, home space. Setting up the environment was one way in which I was able to signal to participants as well as myself that my primary role in the interaction was that of interviewer/researcher.

As the lead researcher, I performed all interviews. Although there was some degree of natural rapport with the US participants since many had been my patients, there was no similar relationship with the UK participants. I felt it was important for the UK participants to have some perspective on my background as part of the rapport building process. They were made aware of my background as a SLT and doctoral student prior to the interviews and I reminded them of this at the onset of our interviews. It was, however, also emphasized that in respect to the interview, my role was that of researcher and not clinician. Interestingly, despite this attempt at role transparency, several participants saw the interview as an opportunity to ask for clinical advice. From an ethical perspective, I needed to acknowledge their desire for information, but maintain clear boundaries about the intention of the interview and the nature of my relationship, not as a clinical provider in this context, but as a researcher. Fortunately, these participants were understanding about this and did not seem to be put off by the delineation of roles. A system had been established apriori to notify the clinical teams through the Liverpool research nurses if any concerning issues arose during these interviews. Participants raising concerns or questions were given the option to have these queries or information passed along to the clinical team.

For participants with which I had a current or prior clinical relationship, I needed to be particularly mindful about role delineation. One of the ways in which I tried to communicate the difference between my usual role as clinical provider and my role as researcher for these interviews was to emphasize that this research was being done as part of my doctoral research. I felt that this admission would contribute to taking me out and placing them into the role of expert. I was very mindful about not referring back to shared experiences in the past even when they seemed pertinent to our discussion. Similarly, I was clear to participants that what we discussed during our interviews was separate to our clinical relationship and that those topics discussed would not be brought up again in the clinical context. When transcribing interviews, I tried to attend not only to the content of the interviews but also any imbalance of talk time and whether my language seemed to be influencing how the participant was responding.

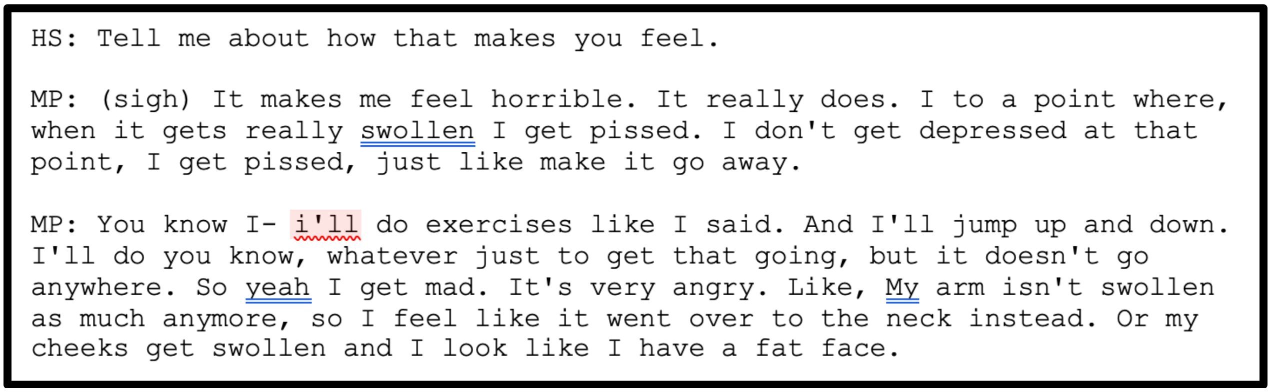
It is important to acknowledge that the format of qualitative interviews may impact the output of the interviews. Prior to the COVID-19 pandemic, use of virtual interviews was uncommon, however with the need to maintain safety in the context of the pandemic, our interviews were all done in a synchronous video format. Historically, remote interviews have been discouraged as it was believed that this format may reduce rapport and limit the content shared by participants (Irvine et al., 2013; Shuy, 2003). However, most of the prior research had focused on comparing in-person and telephone interviews rather than video interactions. Because the use of video-assisted qualitative interviews is an emerging method, there is limited data to suggest whether this format is equivalent, better than, or worse than traditional in-person interviews.

Because of the need to continue research efforts during a global pandemic, there has been increasing interest in use of video interviews in qualitative research. Some have proposed potential logistic benefits that might allow a broader selection of patients to participate, particularly those who are generally underrepresented (Keen et al., 2022; Lathen & Laestadius, 2021). Lobe and colleagues (2020) provided practical suggestions to optimise synchronous video qualitative interviews and to ensure participant privacy and protection. I implemented these suggestions in my research, choosing the Zoom platform, which is easy to use, has privacy protection features, and the ability to get basic, first level transcription of the interview. Though the impact of using virtual interviews is unknown, the willingness of participants to share openly during these interviews was encouraging and suggested that adequate rapport was established, despite the less personal setting. Certainly, I benefitted from being able to interview individuals in two countries which provided some cross-cultural validation to the work. It should be acknowledged that while this method of interviewing was beneficial to those with limitations in regard to travel, it may have limited engagement for those without access to the necessary computing services.

4.10. Preparing the transcript

Orthographic transcription includes the verbatim documentation of spoken words as well as other pertinent vocalisations and sounds. This allows the researcher to not only capture the specific words spoken by the interviewee, but also any other relevant contextual clues that may be necessary when interpreting the underlying meaning of the interview responses (Braun & Clarke, 2013) (Figure 4-7). Because the transcript is a representation of an event, there is potential for information to be misconstrued in the transcription process. As a result, the transcriber needs to exercise extreme caution to minimise potential for inaccurate representation of the interview. Best practice is to complete the transcription as close as possible in time to the interview (Braun & Clarke, 2013). Transcripts should indicate who is speaking, when there are instances of overlapping speech, inaudible or unintelligible utterances, and emphasis stressed by the speaker. The transcriber should be cautious to avoid over-punctuation as this can alter the meaning of the utterance. Transcripts should be anonymised to protect the identity of the participant and any other individuals they may name. It is often necessary to review a transcript several times for quality control purposes. The transcription process may be arduous, but this is critical to ensure adequate representation of the data as the researcher moves into analysis and interpretation. Modern advances in technology offer opportunities for first level transcription using voice recognition/artificial intelligence (AI) methods (Fogg & Wightman, 2000; Matheson, 2007), however these methods are not developed enough at the current time to replace the engagement of the researcher in the transcription process.

Figure 4-7 Example of orthographic transcription



HS: Tell me about how that makes you feel.

MP: (sigh) It makes me feel horrible. It really does. I to a point where, when it gets really swollen I get pissed. I don't get depressed at that point, I get pissed, just like make it go away.

MP: You know I- i'll do exercises like I said. And I'll jump up and down. I'll do you know, whatever just to get that going, but it doesn't go anywhere. So yeah I get mad. It's very angry. Like, My arm isn't swollen as much anymore, so I feel like it went over to the neck instead. Or my cheeks get swollen and I look like I have a fat face.

During my transcription of qualitative interviews, initial transcripts were extracted using AI techniques through the Zoom platform. Although this provided some time benefits, I still reviewed each recording several times to ensure accurate transcription. I took particular care to minimise biases in my transcription that could have resulted from over-reliance on the computer-generated content. Although all sounds and vocalisations were not transcribed, I included those which appeared to potentially impact meaning (such as laughter). It is possible that by not including all sounds, my analysis and interpretations may have been influenced.

4.11. Analysing and interpreting qualitative data

Following a qualitative interview and its transcription, the researcher then embarks on the process of qualitative data analysis. Analysis includes the identification, coding, and categorisation of patterns or themes within the collected data (Braun & Clarke, 2013; Patton, 1990). With inductive analysis, codes and themes are established based on the data and may emerge and evolve over the course of analysis. In contrast, more deductive approaches to analysis may pre-determine codes and categories expected in the data, with assignment of specific data to these pre-determined codes, themes, and categories. It is important to acknowledge that whether inductive or deductive approaches are used, the researcher plays an active role in decision making around the development of codes, themes, and categories (Braun & Clarke, 2021). Themes do not magically emerge from the data.

In contrast to quantitative research, the investigator may choose to engage in data collection and analysis simultaneously to respond to certain themes as they develop. For example, in my qualitative interviews, issues around intimacy and sexuality arose with several participants, but were not included in the initial interview guide. The flexibility of the semi-structured format allowed me to probe more around this concept with subsequent interviews to ensure we had explored it more fully.

The qualitative researcher immerses oneself in the data during early analysis, making notations of observations and impressions of the data prior to formal coding. Transcripts must be systematically and painstakingly reviewed to uncover the meaning of the data, not just the superficial interpretation of words. The investigator may review transcripts several times before proceeding to formal coding.

4.11.1. Transcript coding

Coding is the next step of analysis and is a way for the researcher to identify data that is pertinent to the research question. Data-derived codes use the words of participants and therefore are a more semantic representation of the concept. In contrast, researcher-derived codes involve the investigator’s interpretation of what those words mean. For example, in our interviews, one participant stated," *I literally feel like I had a rope tied around my neck,"* which could stand on its own as a data-derived code or could be "tightness around the neck" as a researcher-derived code. The researcher systematically reviews the transcript, applying codes to portions of the text that are relative to the research question. Following this process, the researcher conducts analysis looking for patterns within the codes to establish more broad themes within the data. See appendix 1 for an example of transcript coding performed for one participant. This initial process of identifying and developing candidate themes benefits from the input of others on the study team prior to finalising themes. I was able to gain the input and insight of my committee members early in the coding process which I felt was quite valuable in validating my impressions and coding choices.

4.12. Analytic methods in qualitative research

There are several different analytic methods commonly employed in qualitative research. The methods employed should be selected prior to completion of interviews. Thematic Analysis (TA), Interpretive Phenomenological Analysis (IPA), Grounded Theory (GT), and Pattern-Based Discourse Analysis (PBDA) are four methods commonly used in qualitative data analysis. For the purpose of this study, I adopted a qualitative descriptive design using reflexive thematic analysis. Thus, the remainder of this chapter will focus on these methods.

4.12.1. Qualitative descriptive design

Qualitative descriptive design is one flexible method that can be used in qualitative studies not requiring rich exploration of theoretical constructs (Doyle, 2020; Neergaard, 2009; Sandelowski, 2000; Sandelowski, 2010). This design is frequently selected when the goal of a project is to provide a rich description of the construct of interest in a clear and concise manner, acknowledging that individual participants will likely have unique perceptions and experiences of the construct of interest (Bradshaw, 2017). Analysis employed in qualitative descriptive studies often aims to provide output that is practical for use by the researcher. For example, in the context of this thesis, the analysis of qualitative data was used to generate items for a PROM. Analysis typically encompasses content and/or thematic analysis approaches. Analysis remains very grounded and near to the data itself, providing an accurate representation of participants' experiences.

Bradshaw and colleagues (2017) provide a description of the philosophical underpinnings of qualitative descriptive studies. They note that studies using this approach do so using an inductive process to develop understanding and/or to describe a construct of interest. This method recognises that the construct of interest can be considered through the subjective experience of participants and that the researcher is an active participant in the research process. This assumes an emic stance where the perspectives of the participants are central to the research question at hand. Finally, they assert that data is collected in the natural setting in which the participant experiences the construct of interest. They state that, "the advantage of a qualitative description approach is that data analysis is more likely to remain true to participants' accounts and contribute to ensuring the researchers' own interpretations are transparent" (p. 5). Thus, given the intent of my qualitative work as a backbone for PROM development, this approach was more appropriate than other qualitative approaches that seek to develop theory (such as grounded theory) or deep interpretation of meaning (such as phenomenology).

4.12.2. Thematic analysis

TA is one method frequently employed in qualitative analysis. This method, which has many variations, can be used to identify themes within a data set and has been described by Braun & Clarke (2006) as offering an "accessible and theoretically flexible approach to analysing qualitative data" (p. 77). It is different from many other methods of qualitative analysis in that it is not constrained by any singular theoretical approach. Because TA is inherently flexible, there are several varieties of analysis within TA. *Inductive TA* allows theory to develop from a bottom-up approach and is guided more by the data than by existing theory. In contrast, *Theoretical TA* uses existing theory as the basis of data analysis. *Experiential TA* focuses specifically on the perspectives and experiences of the interview participants. *Constructionist TA* focuses on how topics of interest are constructed and how an individual's experience influences how they construct their reality. TA is one of the most flexible and accessible methods used in qualitative analysis (Braun & Clarke, 2013).

Over time, there has been some evolution as to how different types of TA may be described. Braun & Clarke (2021) updated their subtyping of TA into three predominant approaches that reflect differences in research paradigms. *Coding reliability* TA is most appropriate for use by researchers with a neopositivist philosophy where there is an emphasis on objective coding using a predetermined codebook to uncover truth. In this approach, it is critical to have multiple coders to calculate reliability data to demonstrate quality of coding. In contrast, *codebook* TA also uses a codebook established a priori, however there is some flexibility to adapt the codebook during the analytic process and reliability calculations are not utilised. This approach is more consistent with qualitative paradigms. The third category, *reflexive* TA uses a more open coding process which is inductive by nature. Thus, reflexive TA more fully embraces the constructivist paradigm.

4.12.3. Analytic approach for this thesis

I selected a reflexive TA approach since the primary goal of these interviews was to identify themes regarding how HNL impacts individual's perceptions of HRQoL. It was critical that the voice of the patient be central in the analysis of transcripts. Whilst my approach to analysis was inductive, it must be recognised that my prior experience with theories of HRQoL influenced analysis to some degree. As Braun & Clarke (2021) stated, "inductive in the sense of analysis 'grounded in' the data, rather than 'pure' induction, because you cannot enter a theoretical vacuum when doing TA" (p. 331). The predominant framework in my rehabilitation model of HRQoL (the WHO-ICF) likely influenced how I approached data analysis. I was mindful of my bias towards HRQoL being comprised of physical, functional, and emotional contributors as I analysed the data. The input of my supervisory team was extremely valuable during analysis to keep me grounded in the patient perspective to minimise the influence of my previous influences. It was quite valuable that two of my supervisors had little knowledge of or experience with HNL as they provided an unbiased perspective to data analysis.

4.13. Interpretation of data

After the data has been coded and arranged into themes, the researcher must then construct a narrative explaining the interpretation of the data. It is a way for the researcher to highlight what is important in the data and why it is relevant to the underlying research question. Often this involves the inclusion of illustrative quotes from the transcripts with some interpretative text explaining how each quote relates to the overall interpretation. Yin (2015) describes 5 qualities indicative of quality interpretation of qualitative data: (1) interpretation is complete, (2) other researchers would reach similar interpretation if provided with the data, (3) interpretations should be representative of the raw data, (4) will add to understanding of the topic being studied, and (5) methods and interpretations should be credible.

4.14. Quality in qualitative research

Braun & Clarke (2006) provided a checklist for quality criteria for thematic analysis which they indicate may also be applied more broadly to qualitative research

(Table 4-3). This checklist includes recommendations in respect to transcription, coding, analysis, overall methods, and the written report. Additionally, in 2021 they provided additional criteria that can be applied for judging the quality of manuscripts using TA. These 20 questions address what the authors see as the most common issues in TA research manuscripts, including considering TA as one singular approach, assumptions around TA being atheoretical and purely descriptive, and confusing themes, codes, and topics.

Table 4-3 Checklist for quality criteria offered by Braun & Clarke (2006)

(With permission from Taylor and Francis)

Process	Criteria
Transcription	Data transcribed in appropriate detail and transcripts double checked against recording for accuracy
Coding	Each data item is given equal attention during coding
	Themes not based only on a few examples, but rather in response to a comprehensive, inclusive coding process
	All pertinent examples for each theme have been selected
	Themes are cross checked and referenced back to the initial dataset
	Themes are coherent, consistent, and distinct
Analysis	Data are interpreted, not merely paraphrased
	Data extracted are reflective of analytic claims
	Analysis tells a well-organised account of the data regarding the research question
	There is a balance between exemplary quotes and interpretation
Overall	All aspects of analysis have been given adequate time and attention
Written report	The specific analytic approach is clearly stated
	What is claimed and what is presented are congruent
	The theoretical position matches the language and concepts presented
	There is acknowledgment of the researcher as an active party in analysis

Yardley (2008) cites additional characteristics or principles that are indicative of quality in qualitative research. These include “sensitivity to context”, “commitment and rigor”, “transparency and coherence”, and “impact and importance”. Just as researchers using quantitative methods must ensure rigor in their work, those employing qualitative techniques must also strive to ensure high caliber work.

4.15. Reflections on qualitative data collection in this study

Qualitative research is something that prior to this work I had limited exposure to or experience with. Though I had participated in a qualitative study of the impact of HNL on caregivers, this was not a methodology that I was overly familiar or comfortable with. Being ensconced in the medical field, the primary research paradigm I have been exposed to is the post-positivist paradigm. In my prior training, the overarching philosophy was that there are defined truths that can be directly measured, though with some degree of error inherent in the research process. I had worked and studied within the bias of quantitative research as being somehow “more than” or “truer than” qualitative work. However, as a clinician, I felt the substantial disconnect between what the quantitative data “told me” and what I experienced working directly with patients. Over the years, it has been increasingly clear to me that in matters of human experience, there is no “truth,” only subjective perceptions. This was the catalyst for my doctoral work and my desire to learn more about qualitative research and paradigms.

As part of my doctoral work, I needed to learn about qualitative research not only from a theoretical perspective, but also from a practical, methodological viewpoint. I enrolled in two courses offered through the Massachusetts Institute of Technology (MIT), ‘Conversational Interviewing’ and ‘Data Coding and Analysis’. These courses were both taught by sociologist Susan Silbey and provided a good foundational understanding of methods used in qualitative research. Additionally, I accessed training through the University of Auckland’s School of Psychology which provides numerous lectures by Professors Braun and Clarke on qualitative research and thematic analysis. I supplemented these through readings such as Braun & Clarke (2013), Charmaz (2014), and Patton (1990). Finally, my supervisory committee provided additional education and training on qualitative research.

My prior clinical experience informed me that there are aspects of the journey of HNC rehabilitation that are poorly understood and interventions that appear to be less effective in the real-world setting than has been reported in the literature (and vice versa). There seemed to be a disconnect between what my post-positivist perspective offered and what I experienced with my patients and their caregivers. Thus, as my research interest in HNL developed, my interest in learning more about qualitative research grew. Embarking on this research has been very enlightening and educational in several ways.

As a clinical provider who has worked with patients with HNC for nearly 25 years and those with HNL specifically for the past 8 years, the process of conducting in depth interviews with patients was quite illuminating. I had prior clinical experience with many of the individuals I interviewed from the US. As such, I had concerns about the potential for participants to censor their experiences and feelings about HNL. It is known that a preexisting relationship between interview participants, particularly when there may be a perceived power differential may lead to hesitation to share on the part of the interview participant (Garton & Copeland, 2010; Roiha & Iikkanen, 2022). What I found instead was that these individuals were extremely forthcoming and willing to be very open about even their most intense emotions and experiences. When given the opportunity and safe space to reflect on their experiences, individuals who I thought were very well adjusted, with limited impact of HNL on their HRQoL, expressed quite dramatic emotional impacts of their HNL. This reinforced the findings of many studies that clinical providers significantly underestimate HRQoL issues in their patients (Bjordal et al.,1995; Jensen et al., 2006) and highlighted the importance of developing an HNL specific HRQoL instrument to help identify such issues and to guide clinical service provision. There was no way for me as a clinician to know the substantial impact of HNL on individuals without specifically exploring those issues with patients directly. It was gratifying to reflect that the rapport I had previously established with these individuals allowed them to trust and be very vulnerable in my presence.

For example, one participant expressed that her HNL weighed heavily on her both physically and mentally throughout the day. She described ways in which it interfered with her job performance and ability to focus. She recalled that many days she was so exhausted from having to compensate for her HNL that she would go to bed upon arrival home, thus limiting her interactions with her spouse and children. She felt that she had neglected her parenting duties and worried that this would have a negative long-term impact on her relationships with her children. At no point during lymphoedema therapy did she express these concerns. Had this been apparent, there would have been an opportunity to engage the assistance of psychological services to help her develop coping strategies and to process the extent to which she felt loss in her most important relationships. Alternatively, we could have focused more on energy conservation during the day to allow her to be more present for her family in the evening. For me, this disclosure reiterated the need to have candid communications with patients about their experiences, and the role that PROMs can have in opening those discussions.

In contrast, there was one participant I recall who appeared a bit more hesitant to share what his personal experiences had been, particularly in response to the emotional aspects of HNL. This individual was one of the younger participants and although he was very forthcoming about the physical aspects of his experience with HNL, he initially seemed reticent to share about his emotional experiences. Much of this revolved around dating and intimacy and his lack of self-confidence. Whilst he was guarded in what he shared, this raised the importance of exploring these issues in future interviews, which was one of the most significant changes made to the interview guide over the course of the interviews. It allowed me to get a better perspective of this very important aspect of HNL impact on HRQoL.

Another interesting reflection from these interviews was in respect to differences between participants from the UK and US. In many cases, participants from the UK were aware that their oncologist had diagnosed them with HNL, but they did not know what options may be available regarding treatment. Because they did not have awareness of the potential for elimination of the HNL, they appeared to have a greater sense of acceptance of the HNL. They presented with a more stoic affect and reported a lesser impact on HRQoL than was expressed by many of the patients from the US.

This highlighted the potential impact of environmental, societal, and other external impacts on HRQoL and the importance of not assuming more severe HNL equates to more severe impairment of HRQoL – we must learn from our patients how they are experiencing, struggling, and coping with this or any other condition.

Engaging in qualitative research was a wonderful learning experience about how different paradigms and methodologies may be appropriate depending on your research question. It is clear to me that answering questions about HRQoL and patient experience at an individual level requires a qualitative approach. Further, learning about qualitative research methods has highlighted that such methods are not “soft science” and require a similar level of rigor and planning as is used in quantitative science.

4.16. Chapter summary

QoL is the reflection of an individual’s perceived overall well-being and can be influenced by physical function, participation in meaningful activities, and psychosocial wellness. HRQoL, in contrast, refers to QoL specific to health status. Individuals with conditions like HNL may have varying impacts on HRQoL due to their medical condition, but HRQoL may also be impacted by personal and external influences. To truly understand the impact of a condition on an individual, one must seek information that is grounded in the patient’s personal experience. Qualitative research is uniquely suited for answering questions about the patient perspective. By implementing systematic qualitative methods, a researcher can gain greater insight into themes and concepts specific to a patient population. These qualitative methods should not be considered as “less than” quantitative methods, but rather an alternative methodology suited for specific research questions, such as those involving questions about HRQoL. The reader is referred to Chapter 6 for more details of the qualitative interviews performed as part of this research.

5. Patient reported outcome measures: development and utilisation

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5.1. Chapter introduction

Patient reported outcome measures (PROMs) are one method for gauging the impact of a disease or condition on an individual’s HRQoL. PROMs are widely used in both clinical and research applications. It is not realistic from a logistic standpoint to systematically employ qualitative interview methods with each patient seen in a clinical setting to identify their specific concerns. Therefore, PROMs are used as a more efficient technique to identify patient concerns which can then be interrogated to a greater extent in the clinical setting. From a research perspective, PROMs allow research teams to integrate patient perceived outcomes in a systematic way for clinical trials and other research endeavors. This chapter will review important aspects of PROM development including item generation, testing, and validity and reliability testing. Chapter 7 will describe the methods employed during this thesis towards PROM development as well as the results of that research.

5.2. Benefits of patient-reported outcome measures

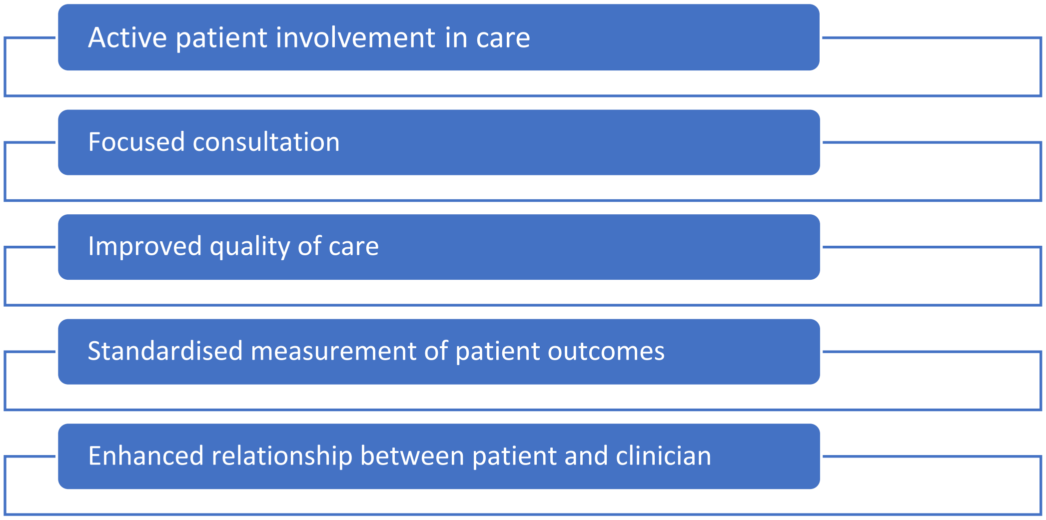
Historically, PROMs have been utilised in clinical outcomes research as a method to establish intervention effects. The use of PROMs in this context has steadily increased in clinical trials registered at ClinicalTrials.gov from 14% in 2004-2007 to 27%

in 2007-2013 (Scoffins & Patrick, 2009; Vodicka et al., 2015). PROMs offer the benefit of assessing the patient perspective in a systematic manner to minimise potential bias and misestimation of treatment impacts (Mercieca-Bebber et al., 2018). Multiple professional societies endorse the use of PROMs in outcomes research including the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), the National Cancer Institute (NCI), and the European Organisation for Research and Treatment of Cancer (EORTC) (Bottomley & Aaronson, 2007; Minasian et al., 2007).

In recent years, there has also been an increased emphasis on using PROMs within clinical practice to help guide patient care and to determine the efficacy of interventions. As with research, many guidelines support the use of PROMs in the clinical setting (Di Maio et al., 2022; Smith & Jensen, 2019). PROMs may be used to screen for specific conditions such as anxiety, to identify patient priorities for treatment (e.g. pain control), and to monitor changes over time. They may be considered a cornerstone of patient-centered practice. PROM use has been associated with higher levels of patient satisfaction as well as improved health outcomes (Barbera et al., 2015; Basch et al., 2017; Licqurish et al., 2019). It has been repeatedly demonstrated that clinical providers underestimate the symptom burden experienced by individual patients (Remick et al., 2020). As such, PROMs play an important role in the accurate estimation of symptom impact on individual patients.

Campbell et al. (2022) performed a systematic review of qualitative studies of patient and provider experiences using PROMs in clinical settings. They used thematic analysis to synthesise the findings of the 50 studies that met their inclusion criteria. Five primary themes were identified regarding potential benefits to use of PROMs in a clinical setting (Figure 5-1).

Figure 5-1 Potential benefits to using patient reported outcome measures in a clinical setting



One overarching benefit identified was that PROM use encouraged active patient engagement in their health care. Both patients and providers felt that use of PROMs allowed for identification of patient needs and symptoms which facilitated a focused consultation and goal setting within the visit. Depending on the nature of the PROM, some studies identified that PROMs may enable a patient to bring up sensitive topics such as sexuality or intimacy. In addition to benefits in patient engagement, PROMs were reported to assist providers in focusing consultations to prioritise patient needs. This may yield improvements in patient care through timely diagnosis, holistic management, and expedited action. Clinicians also reported that PROMs improved their ability to monitor patient outcomes over time. This was seen to assist with determining treatment efficacy as well as identifying any negative sequela of treatments. Some patients and clinicians felt that PROMs could be used to facilitate the patient-provider relationship. In contrast, some patients felt that PROM use minimised meaningful interactions with their providers, whilst some providers felt that PROM data may not be sufficiently meaningful to guide clinical decision making.

Another qualitative study looking at surgeons' perceptions of PROM use in clinical practice identified perceived benefits in patient care, but also the need for institutional support and an optimised integration platform to increase the feasibility of successful integration into the clinical setting (Driscoll et al., 2022). These studies identify potential benefits of PROMs in clinical practice, but also some concerns that need to be taken into consideration in implementation when integrating PROMs into a clinical setting.

5.3. Integrating patient-reported outcome measures into clinical practice

Routine use of PROMs in clinical care remains limited despite the benefits associated with their use. Recommendations have been provided to optimise implementation of PROMS into clinical practice (Mazariego et al., 2022). The most prioritised recommendations prior to integrating PROMs included assessing the readiness of the clinic to implement PROM use, addressing barriers that may interfere with implementation, developing implementation strategies, monitoring use and evaluating outcomes, and developing strategies to support sustainability. Antunes et al.

(2013) provided specific recommendations at the management, provider, and patient level to facilitate successful implementation of PROMs into clinical practice. One concern that may be raised is that the PROM might identify an unmet need for which services are not readily available. For example, if psychological services are not available, identifying substantial depression may raise challenges for the clinical team. Such issues should be identified and discussed prior to implementation of PROMS in the clinical setting.

One consideration is the format in which they will be offered. Historically, PROMs were administered through paper surveys, however in recent years there has been increasing interest in PROM completion through electronic options. A Cochrane review by Belisario et al. (2015) demonstrated that electronic PROM administration (app and SMS based) was comparable to paper administration for data equivalence. Though some of the studies included in this review demonstrated greater efficiency of the electronic PROMs (ePROMs) as well as more complete data entry, this was not a consistent finding. These authors and others (Bliven et al., 2001; Chang, 2007; Holmes et al., 2019) advocate for consideration of ePROMs to streamline clinical implementation of PROMs. Ideally, these ePROMs could be integrated into the electronic medical record to facilitate access by the care team over time (Hunter et al., 2015).

A key factor that needs to be determined to optimise implementation of PROMs into clinical practice is determining what the PROM will be used for. Without a clear vision of the intent and value of the PROM, it is unlikely that there will be adequate buy in from the clinical team (Roberts et al., 2019). Clinicians need to understand why and how the PROM may benefit their patients and clinical practice (Antunes et al., 2013). A clinical care team needs to determine, apriori, what they will use the PROM for: tracking individual change over time, identifying targets for treatment to provide person-centred care, tracking change in response to a treatment, or demonstrating “quality” of the health care system (Benson, 2022).

5.4. Defining the goal of a patient-reported outcome measure

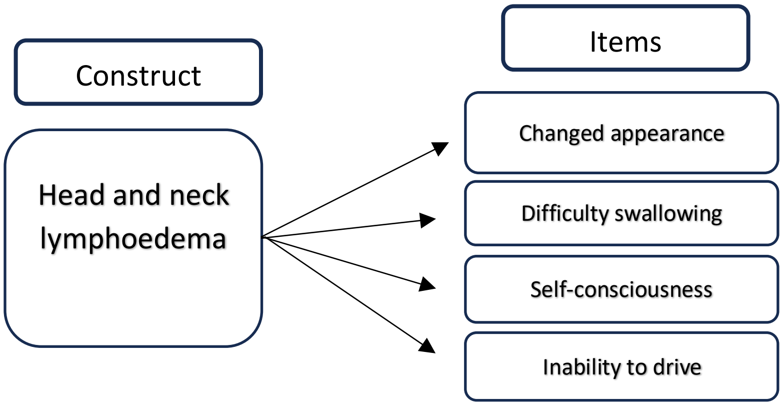
Diagnostic measures in medicine commonly focus on the physical and physiologic level of abnormality or impairment. This includes tests such as blood work and radiographic imaging. In the case of HNL, these measures would include things like tape measurements and clinician-rated oedema severity scales. Diagnostic measures are considered to be objective and often quantifiable. It is important to note, however, that many diagnostic tests rely on the subjective interpretation by a practitioner. Thus, even these purportedly objective measures have some degree of subjectivity.

In contrast to these diagnostic tests, PROMs focus on the impact of the medical condition from the patient perspective and measure symptoms that can only be experienced by the patient themself.   As patient experiences are subjective by nature, there are challenges to quantifying them in a similar manner to other medical diagnostic tests. Within the realm of PROMs, assessments may focus on either the presence of specific symptoms or more broadly on the impact of those symptoms across domains. Prior to development of a PROM the researcher needs to determine what is the construct they wish to measure, in what population, and for what purpose. These determinations will heavily influence the appropriate conceptual framework to apply. Tools may be considered discriminative, evaluative, or predictive. Discriminative tools are designed to differentiate between people with and without the construct of interest, whilst evaluative tools are meant to measure change over time and predictive tools are designed to predict future outcomes.

5.5. Reflective and formative models for patient-reported outcome measure development

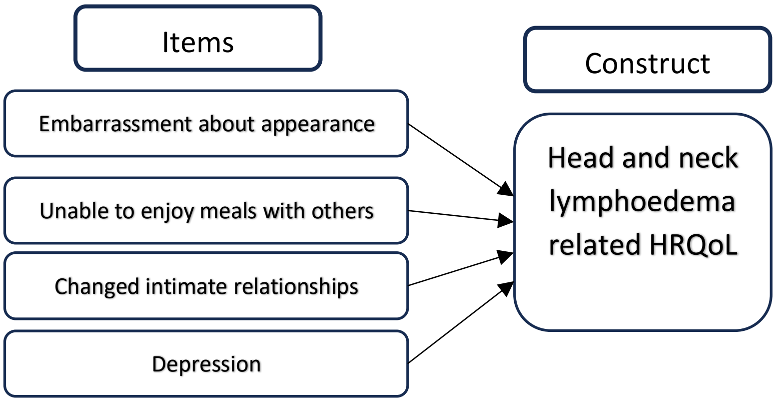
The two most common frameworks in PROM development are the reflective model and the formative model. These conceptual frameworks help to define the relationship between the construct of interest and the items used in the PROM. In reflective models, the construct of interest is reflected in the items developed. In other words, the items are chosen to reflect the effect of the construct on the individual. This is depicted in Figure 5-2. In a reflective model, if the construct changes, it is expected that the expression of the each of the items will also change. For example, as HNL increases, one would expect alterations in appearance to likewise change. Symptom inventories generally follow a reflective model.

Figure 5-2 Example of a reflective model applied to head and neck lymphoedema



In contrast to the reflective model, in a formative model, the items are causally related to the construct of interest. The formative model is represented in Figure 5-3. In the formative model, a change in the construct does not necessarily result in a change in each item. For example, though HNL-related aspects of HRQoL may worsen for a patient, that does not necessarily mean that their experience with intimate relations would be changed. HRQoL PROMs generally follow a more formative model, though HRQoL is complex and may include both reflexive and formative components.

Figure 5-3 Example of a formative model applied to head and neck lymphoedema



Jarvis et al. (2003) provide a model for determining whether a particular test is more likely to be reflective or formative. The following seven characteristics are useful for determining when an item is formative.

1. The items are viewed as defining characteristics of the construct.
2. Changes in the items are expected to result in changes in the construct.
3. Changes in the construct are not expected to result in changes in the items.
4. The items do not necessarily share a common theme.
5. Eliminating an item may alter the conceptual domain of the construct.
6. A change in the value of one of the items is not necessarily expected to be associated with a change in all the other items.
7. The items are not expected to have the same antecedents and consequences.

I selected a formative model for PROM development in this thesis as the primary construct of interest is HRQoL related to HNL and the indicators are judged to be contributors to HNL related HRQoL and fit within the criteria provided by Jarvis.

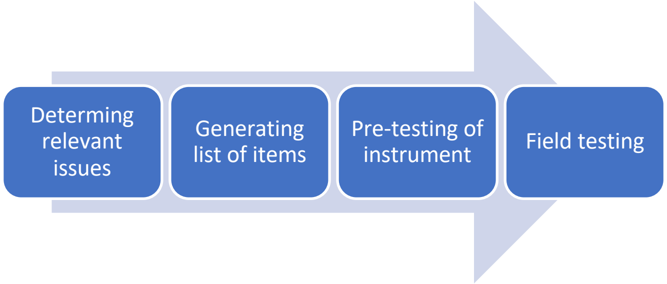
5.6. Patient-reported outcome measure development stages

Prior to developing a new PROM, it is important to first understand the available tools that might be suitable for the stated need. The systematic review described in Chapter 3 was performed to better understand the available options for measuring HNL and HNL specific HRQoL. I was unable to identify a tool I felt was suitable for identifying and measuring HRQoL impacts of HNL from a formative perspective, and as such, I opted to develop a tool specifically for this purpose. In particular, I identified a need to measure the emotional and social impacts of HNL. This need was confirmed and validated in my informal conversations with Dr. Barbara Murphy, one of the lead developers of the HN-LEF Symptom Inventory. She agreed that the inability to capture and measure the emotional impact of HNL is a shortcoming in the currently available tools used in HNL management.

Increasingly, it is recognised that patient participation in the development of PROMs is critical and likely underutilised (Basch et al., 2015; Wiering et al., 2016). Failure to engage patients in the development process can have a detrimental impact on the validity of the measure due to failure to identify and incorporate important contributors to HRQoL. Similarly, clinical experts should be engaged at multiple stages of instrument development. Including both patients and clinician experts contributes to the content validity of a measure and to the functionality of the instrument within clinical and research settings. At the very least, patients and experts should be involved in determining the outcomes of interest to be measured, in generating items to reflect those outcomes, and in testing the instrument to ensure it is easy to understand.

The EORTC described 4 primary stages of PROM development (2011) (Figure 5-4). Phase 1 involves the generation of a comprehensive list of relevant issues pertaining to the construct of interest. Phase 2 represents the development of the item list. Phase 3 involves pre-testing of the pilot instrument. Phase 4 includes field testing of the instrument. Each of these sequential phases will be detailed in the following sections. Chapter 7 will provide further detail regarding the methods used in PROM development for this thesis.

Figure 5-4 Stages of PROM development according to the EORTC



5.6.1. Quality of life issue generation

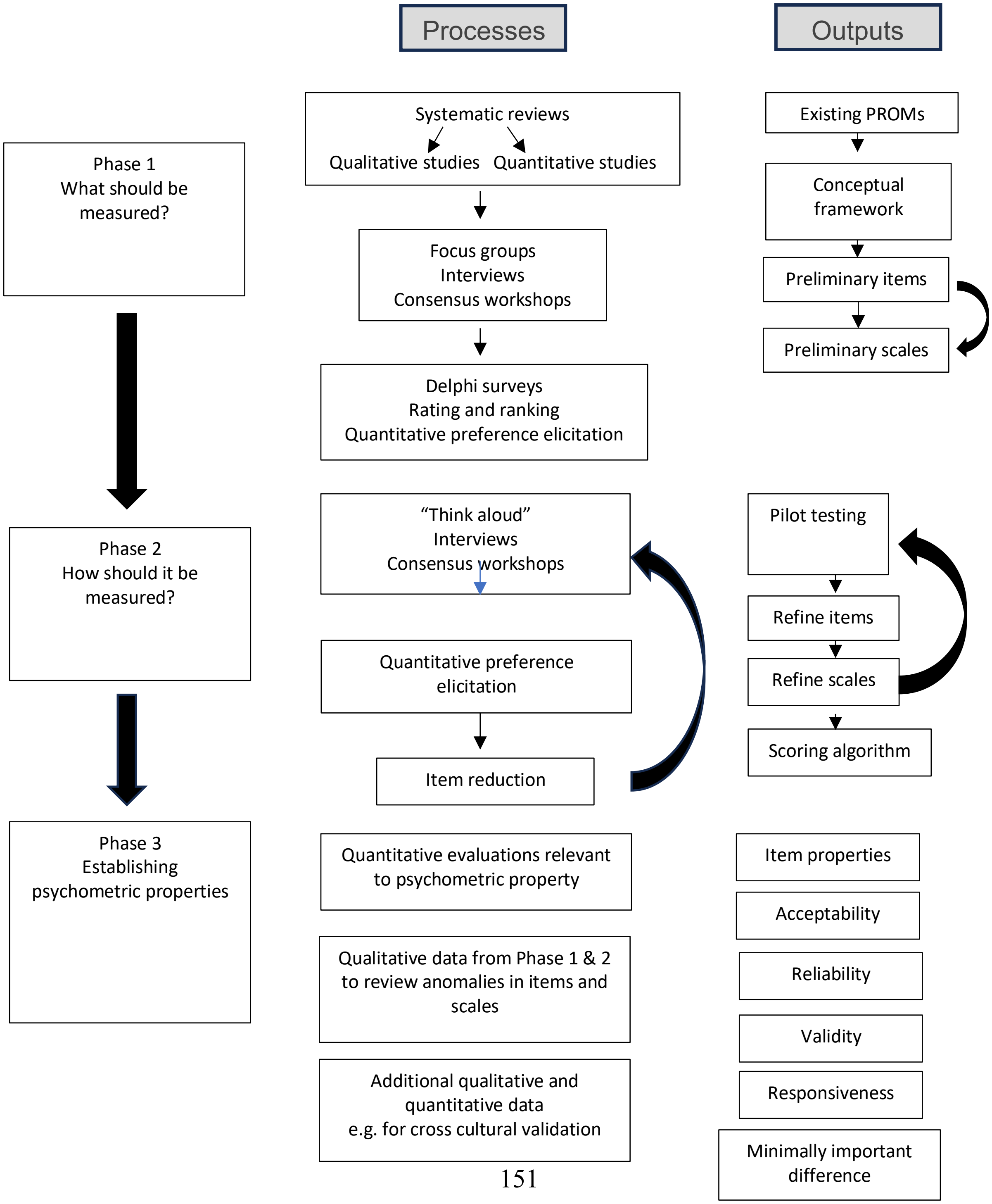
Determining the pertinent issues to measure requires thoughtful and iterative consideration of the construct of interest from multiple viewpoints. The initial step should involve a review of the literature and existing instruments (See Chapter 3). During this review, a comprehensive list of all identified questionnaires and HRQoL issues should be compiled. Based upon this information, interviews with patients and clinical experts may proceed for further item generation and consideration of relative importance of different items.

5.6.1.1. Patient feedback

PROMs are intended to measure a construct that only the patient can report on. As a result, it is critical that patient perspectives be considered in the development of a PROM. Qualitative research methods are key to ascertain those patient perspectives. Howell et al. (2022) provided an adapted framework for PROM development based on earlier works by Wong Riff et al. (2017) and Rutherford et al. (2017) (Figure 5-5). In this model, qualitative methods are integrated into each stage of development, however most critically in Phase One when determining what should be measured. They state, “qualitative measures are used to explore the meaning, experience, and impact” of the construct of interest. Items should be generated based on the lived experience of patients experiencing the construct of interest. Such qualitative data may be obtained through semi-structured interviews, focus groups, and surveys. Including the patient experience at this stage of development is critical to achieving content validity. Chapter 4 provides an in-depth discussion of qualitative methods utilised during this process.

Figure 5-5 Patient-reported outcome measure development process by Howell et al. (2022)

(Reprinted from Methods Volume 205, Howell et al., The critical role of mixed methods research in developing valid and reliable patient-reported outcome measures. P 214. 2022. With permission from Elsevier)



5.6.1.2. Clinician/expert feedback

In addition to considering the patient perspective, there is value in incorporating expert clinicians' views on the identified concepts to ensure the breadth and depth of the construct are represented. The concepts identified through the literature review and through patient interviews may be presented to clinicians with expertise in the target population/condition. This can take the form of semi-structured interviews or through surveys inquiring about the relative importance of each concept and whether there are any missing concepts. If there are discrepancies between patients and clinicians, the patient's perspective should generally be given priority (deVet, 2011).

5.6.2. Item list construction

Once a comprehensive list of relevant concepts is developed, item generation and refinement may proceed. Whilst there may be times when existing items may be utilised from existing scales, it is often necessary to construct new items for a PROM. Bradburn et al. (2004) cited basic rules that should be followed when constructing PROM items.

- Items should be understandable regardless of education level. In general, the reading level should be appropriate for those 12 years of age.
- Terms with multiple possible meanings should be avoided.
- Items should be specific.

- Each item should include only one question. Compound questions such as "When I am swollen, I am unhappy with my appearance and as a result I do not go out of the house" should be avoided.
- Negative wording should be avoided.

PROMs are developed taking into consideration the overarching construct and its component latent variables. Typically, the overarching construct of HRQoL is difficult to define and directly measure. As a result, items consist of latent variables which contribute to HRQoL. Thus, the majority of HRQoL instruments are multidimensional, including several distinct aspects of HRQoL such as physical function, psychological well-being, and social participation. HRQoL PROMs often include a single global question meant to ascertain the gestalt patient perception of their HRQoL such as "overall, how has your quality of life been in the past week." Given the complexity of the construct of HRQoL and the variable definitions likely to be employed by clinicians, researchers, and patients, most HRQoL PROMs also include multiple component items that are believed to represent the overall construct of interest. Appendix 2 provides the initial item list I constructed from reviews of the literature and qualitative interviews.

As formative models are commonly employed in development of HRQoL PROMs, it is critical to include all variables that may influence the construct of interest. It is particularly critical to include those items most frequently cited as important to patients. Similarly, it is important to eliminate items that are not relevant to the construct of interest to maintain test validity. Once an item list is generated, patients and expert clinicians can again be asked to review these items and provide input on their clarity and importance. It has been recommended that 3-10 stakeholders be engaged in this process (Gilbert, 2016).

5.6.2.1. Content Validity Ratio

Lawshe's Content Validity Ratio (CVR) can be used to quantify the relative significance of individual items on an instrument. To calculate CVR, participants are asked to rate items according to how essential they feel each item is to include in an instrument. A numeric value is given to each score (e.g. a score of 0 indicates an item is not important and a score of 4 indicates an item is very important). The CVR is calculated as per Figure 5-4. CVR values range from -1.0 to +1.0 where lower scores denote unimportant items and higher scores indicate more important items. Lawshe (1975) recommended a cutoff score of ≥0.62 for a specific item to be included in a scale. Ayre & Scally (2014) proposed a new recommendation for CVR cutoffs derived from expert panels ranging from 5-40 participants based on a belief that there may have been issues in the initial calculation of cutoff scores provided by Lawshe, and under the assumption that binomial probabilities should be used when considering CVR.

Figure 5-6 Calculation of Lawshe's Content Validity Ratio

$$\boxed{CVR = \frac{n_e - N/2}{N/2}}$$

Where n_e= number of raters identifying an item as essential and N=the total number of raters

5.6.2.2. Binning and winnowing

Another method that may be employed to refine an instrument is the process of binning and winnowing (Dewalt et al., 2007). Binning is a systematic process used to collate candidate items with shared meaning. For example, “HNL impacts my neck mobility” and “My neck is stiff due to HNL” might be binned together as items that refer to neck function. Once candidate items are binned into different construct groups, winnowing may be conducted to eliminate items judged to be like other items. Winnowing may also eliminate items judged to be irrelevant to the construct of interest, too narrow to apply to a broad population, or otherwise judged to be unnecessary. This process allows the PROM to be comprehensive without being redundant.

5.6.3. Response and scoring options

In addition to generating items, response format and scoring options must also be taken into consideration. The most common scoring options include nominal, ordinal, and interval scoring. Nominal and ordinal scoring are used for categorical variables, whilst interval scoring is used for continuous variables. Nominal scoring includes options that do not have a clear order, for example physical location of oedema (face, submental region, neck). Ordinal scoring includes options that have a clear order, for example severity levels of lymphoedema (none, mild, moderate, severe). Likert scales are an example of ordinal scoring where options are provided for more attitudinal concepts where there is not necessarily a right or wrong answer. For example, a range of options from “strongly agree” to “strongly disagree” might be used when asking questions about impacts on HRQoL. Likert scales typically offer an odd number of options with the middle option representing a neutral response. In contrast, interval scoring uses numerically measured outcomes such as a tape measurement of an oedematous structure. For a concept like HRQoL, ordinal options are commonly implemented. The number of options presented for a psychosocial ordinal scale usually ranges from 3-7 as it may be difficult to distinguish differences when more than 7 options are provided (Miller, 1956).

5.7. Pilot-testing

Once a beta version of a PROM has been developed, pilot testing is performed to ensure the instrument is understandable, comprehensive, and practical. Pilot testing must involve the target population. Cognitive interviewing is a qualitative method commonly used during pilot testing. This involves asking the participant to complete the PROM whilst providing insight about how they interpreted and responded to questions. Two methods often used in this process are the “think aloud” method and “probing” methods. When using the “think aloud” method, participants are asked to verbalise exactly what they are thinking as they are reading the PROM questions and deciding on their answers. This method relies on the participant to provide this information and contextual information. In the “probing” method, the researcher guides conversation by asking the participant about how and why they selected certain responses. The “3-step interview” combines these approaches, allowing the participant to first share their thoughts, followed by probing by the researcher to further enhance understanding of the patient perspective, and concluding with the interviewer providing a debriefing and synopsis of the first two stages of the interview.

In addition to understanding how individuals interpret questions on a PROM, pilot testing can be helpful for validation of response options, testing format, instructions, and how practical the PROM may be in implementation (Rothrock et al., 2013). All of these can be probed during cognitive interviews. A researcher may also choose to engage expert clinicians in pilot testing, particularly regarding questions about implementation and feasibility (deVet et al., 2018).

5.8. Field testing

Following instrument development and pilot testing, field testing is often utilised to further validate the PROM. Field testing typically involves much larger, more heterogenous samples than are typically used in early stages of PROM development. Field testing often involves quantitative analysis based on the participation of >100 participants. As field testing was not intended to be a part of this thesis, field testing will be outlined in greater detail in Chapter 8 during my discussion of future directions.

5.9. Assessing quality of PROMs: COnsensus- based Standards for the selection of health Measurement INstruments criteria

The COnsensus- based Standards for the selection of health Measurement INstruments (COSMIN) criteria were developed to provide a framework by which studies on health measurement instruments can be assessed. Development of the COSMIN checklist included the input of 57 international experts with experience in health measurement (Mokkink et al., 2010a). They utilised a Delphi approach to establish a taxonomy for measurement properties of instruments designed to assess patient-reported outcomes. The three main domains selected as critical to a quality PROM were reliability, validity, and responsiveness. Figure 5-7 provides a graphic representation of measurement properties that should be considered during PROM development.

Figure 5-7 COSMIN measurement properties to consider for PROM development

(Reprinted from the Journal of Clinical Epidemiology Volume 63, Number 7. Mokkink et al., The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. p 741. 2010. With permission from Elsevier)

5.9.1. The COnsensus- based Standards for the selection of health Measurement Instruments risk of bias checklist

The COSMIN risk of bias checklist can be used to rate the relative quality of the methods used to develop an instrument (Mokkink et al., 2018). Although it was developed to assess the quality of methods once a PROM development study has been published, it can also serve as a useful reference during PROM development to optimise quality prospectively. The checklist includes 10 boxes:

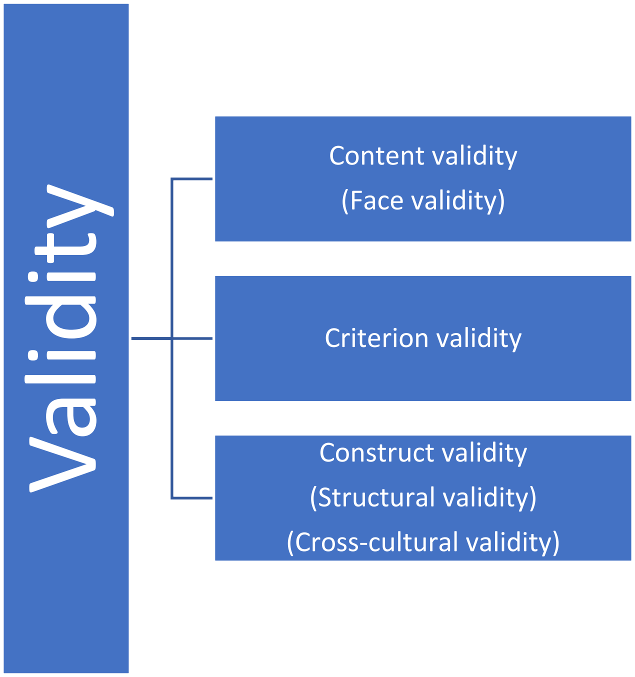
1. Standards for PROM development (35 items)
2. Content validity (31 items)
3. Structural validity (4 items)
4. Internal consistency (5 items)
5. Cross-cultural validity/measurement invariance (4 items)
6. Reliability (8 items)
7. Measurement error (6 items)
8. Criterion validity (3 items)
9. Hypothesis testing for construct validity (7 items)
10. Responsiveness (13 items)

Each item within the checklist is rated as “very good”, “adequate”, “doubtful”, “inadequate”, or “n/a”. A full user manual and the checklist can be accessed at the COSMIN website, www.cosmin.nl.

5.10. Validity

The validity of an instrument refers to whether the instrument truly measures what it aims to measure. Within the realm of validity, there are several specific types of validity that need to be considered, described below and in Figure 5-8. To determine the validity of a measure, there must be a clear definition of exactly what the construct of interest is. For example, in the current research I am operating under the definition of HRQoL as the interaction of physical, functional, and socioemotional outcomes on patient perceived well-being. Thus, the instrument under development needs to include items that span all three domains to be considered a valid representation of the construct of HRQoL.

Figure 5-8 Types of validity



5.10.1. Content validity

COSMIN has defined content validity as “the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured” (Mokkink, 2010). Face validity is a component of content validity and is an overall impression as to whether an instrument appears to be an appropriate reflection of the construct of interest. Determining face validity is a subjective process that does not involve any in-depth methods or analysis. Even though this is a subjective consideration, it is a critical first step in determining whether a measure is likely to provide the information needed to measure a construct.

Once face validity is established, content validity needs to be considered in a more rigorous fashion. The underlying question is whether the instrument is both relevant and comprehensive to measure the construct of interest. A critical aspect to establishing content validity is engaging expert stakeholders to assess the validity of the instrument. This can be done by engaging clinical experts, but in the case of a PROM, should ideally also involve the input of patients. Content validity generally is a qualitative determination which does not rely on statistical analysis. Chapter 7 will provide greater details regarding the processes utilised in this thesis to establish content validity of the PROM under development.

5.10.2. Criterion validity

Assessment of criterion validity refers to how well the instrument correlates with a gold standard measure of the construct of interest. This assumes that a gold standard for the criterion exists. Criterion validity includes concurrent validity (demonstration of criterion validity at a single point in time) and predictive validity (the instrument can predict the gold standard at a future time). In the case of HRQoL related to HNL, no gold standard measure exists, therefore it is not possible to establish criterion validity.

5.10.3. Construct validity

When a gold standard for the construct of interest is not available, construct validity becomes more critical. Construct validity refers to the extent to which the scores of an instrument are consistent with hypotheses. For example, I hypothesise that scores on the PROM under development will correlate to overall QoL/HRQoL scores. Therefore, construct validity would determine to what extent this hypothesis is valid. Plans for establishing construct validity in future research are described in Chapter 8. Within the domain of construct validity, the COSMIN group included structural validity, hypothesis testing, and cross-cultural validity. Structural validity refers to “the degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured” (Mokkink et al., 2010b). Factor analysis is frequently utilised to determine structural validity. Hypothesis testing may include techniques to establish convergent validity (positive correlations with similar constructs) or discriminant validity (lack of correlation with dissimilar constructs). Cross-cultural validity refers to whether a translated instrument performs similarly to the original instrument. Chapter 8 will outline plans for future validation work.

5.11. Reliability

Reliability is defined as “the degree to which the measurement is free from measurement error” (Mokkink, et al., 2010b). It refers to scores that do not vary when the test is repeated under similar conditions. For example, if an individual took the same test at two different time points when the construct of interest had not changed, you would expect the scores to be similar. In other words, reliability refers to the consistency of an instrument to provide similar reflection of the construct of interest. The domain reliability encompasses internal consistency, reliability, and measurement error. Details regarding plans for future reliability testing will be discussed in Chapter 8.

5.12. Responsiveness

Responsiveness is like validity, but specifically refers to the validity of a score change. In other words, how well the tool can detect a change in the construct of interest. To measure the responsiveness of an instrument, a longitudinal study including at least two measures at different points in time is required. The key to responsiveness studies is ensuring a proportion of participants would experience true change in the construct of interest between the two time points. It is important to understand the minimally important change (MIC) of a measure in order to judge relevant change over time or in response to a treatment. A discussion of potential responsiveness studies will be included in the “future directions” portion of Chapter 8.

5.13. Chapter summary

PROMs provide insight into those things which cannot be directly observed. Hence, they are particularly valuable for measuring the psychosocial impacts of conditions such as HNL. PROM development should include a systematic process, engaging key stakeholders at all phases of development, including item construction and survey optimisation. Care should be taken to address issues around validity during instrument development. Instrument testing should be performed to establish the validity, reliability, and responsiveness of a measure.

6. Qualitative interviews (Published paper)

6.1. Study rationale

Despite my clinical experience working with individuals with HNL, it was critical that patient perspectives were central to the development of an HNL-specific HRQoL PROM. Though there are previously published qualitative and survey-based studies available to provide some insight into the impact of HNL on HRQoL (Deng, Murphy, et al., 2013, McGarvey et al., 2013, Nixon et al., 2018), it was important that we accessed a wider variety of perspectives for our study. As discussed in chapter 2, a primary limitation to earlier qualitative studies was the inclusion of a relatively homogenous patient population (middle-aged White participants with oral or oropharyngeal cancer) sampled from single institutions. In the context of trying to develop a valid and representative PROM, a more heterogenous sample is desirable. Thus, I felt it was important to sample from a diverse population to identify as many potential impacts HNL may have on HRQoL as possible. I used purposive sampling to ensure we had perspectives from a wide range of individuals differing in age, sex, ethnicity, country of origin, and socioeconomic status. Further, I sought to include participants with different primary tumour sites, oncologic treatments, and time elapsed since treatment. By engaging a heterogenous sample, I felt I was more likely to have a comprehensive understanding of possible impacts of HNL on HRQoL to guide PROM development of an instrument suitable for a diverse range of patients.

6.2. Comments on study methods

Qualitative interviews were completed in the height of the COVID-19 pandemic (June 2021-August 2022). As such, all interviews were performed via the Zoom video platform rather than in person. Whilst this may have negatively impacted my ability to establish rapport with participants, it allowed for sampling across two countries which contributed to my aim of having a more diverse population. It is also possible that because these Zoom interviews were performed in the home environment at a time convenient to the participant, it increased the potential for interviews of individuals who might otherwise be underrepresented due to an inability to travel or take time off from work.

Following completion of this study, I had the opportunity to read deeper into some more recent philosophies regarding the concept of data saturation. Data saturation was initially proposed by Glaser and Straus (1967) as part of Grounded Theory methodology, with a positivist assumption that a point could be reached when the "truth" was established. Braun & Clarke (2019, p. 202) describe this as suggestive of "completeness of understanding and a determinable, fixed point for stopping data collection." Recent discussion has raised concerns that this assumption is not consistent with the constructivist paradigm frequently associated with qualitative research and thematic analysis (Braun & Clarke, 2019; Thomson, 2021; Varpio, et al., 2017). Other authors have advocated for consideration of "theoretical sufficiency" as a guideline for sampling in qualitative work to reflect that there is *adequate* data for the purpose of the investigation rather than an *exhaustion of all possible relevant data* (Dey, 1999). This resonates with Malterud's "Information Power" (2016) where the emphasis is on the quality rather than the quantity of the data collected. In addition to these theoretical issues with data saturation, from a practical perspective, Clarke ponders how can a researcher determine theoretical saturation before analysis is completed? (Thomson, 2021). In other words, if analysis and theme generation is performed after data collection, there would be no way for a researcher to determine that no new themes might emerge from additional interviews.

I have reflected upon these questions around data saturation and how I conceptualized this within the context of this study. While transcription was completed alongside data collection, actual coding was completed following completion of all transcriptions. Thus, the practical question about data saturation is well taken. While it appeared that no new themes were emerging during later interviews, it is possible that with formal analysis and interpretation, this may not have been the case. But more importantly, particularly given the goal of this qualitative study, it is critical that I understand that while I feel the interviews elicited a sufficient data set for the purpose of this study, there is no way to ensure that no other themes may have emerged if additional participants were included. This emphasises the importance of other aspects of the PROM development process such as stakeholder surveys and cognitive interviews that will be discussed further in Chapter 7. These steps are critical to ensure that important contributors to HNL related HRQOL are included in the CALI-HaN.

6.3. How this study informed subsequent research

These interviews identified physical, functional, social, and emotional impacts of HNL on participant HRQoL. This supported my hypothesis that there are socioemotional impacts of HNL not captured by extant PROMs. The themes developed from these interviews were the basis of item generation efforts for the HNL-specific HRQOL PROM which will be discussed further in Chapter 7. Initial items were generated using the specific language of the participants of this qualitative study (Appendix 2). These interviews provided perspective regarding the breadth of issues associated with HRQoL in individuals with HNL, but also the universality of some of the concerns that were reported by most participants. This provided me with initial impressions regarding relative importance of different items to be explored in the next stage of this research. For example, a sense of vulnerability was commonly reported, suggesting this would be an important item to include in the PROM.

Additionally, through these interviews I was able to hear directly from patients about those issues they felt were inadequately addressed by their clinical teams. These insights emphasised the importance of creating a tool that would facilitate improved communication between patients and their care providers. Thus, in the next stages of research I intentionally sought out the opinions of both patients and clinical providers about implementation of the PROM in a clinical setting. Although the primary intent of this thesis was the initial development of a PROM rather than its implementation, I felt it was important to consider the feasibility and utility of this instrument from the onset of development.

6.4. Presentation and publication

6.4.1. Presentation

Quality of life in head and neck cancer survivors with head and neck lymphoedema: a qualitative study to inform the development of a patient-reported outcome measure. Starmer, H.M., Cherry, M.G., Patterson, J., Fleming, J., Young, B. (11/2022). Annual Quality of Life in Head and Neck Cancer Conference. Leeds, UK.

6.4.2. Publication

Journal: Supportive Care in Cancer

Status: Published

Submission date: 15 March, 2023

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6.5. Contributions

Heather Starmer conceived and designed the study and the initial interview guide, performed and transcribed qualitative interviews, analysed qualitative data, and drafted the manuscript under the supervision of Joanne Patterson, Jason Fleming, Gemma Cherry, and Bridget Young. Gemma Cherry and Bridget Young provided substantive feedback regarding the interview guide and participated in thematic analysis of interview data. All authors contributed to development of the manuscript and approved the final article.

6.6. Published study

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Head and neck lymphedema and quality of life: The patient perspective

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Abstract:

Purpose: Head and neck lymphedema (HNL) is common after head and neck cancer (HNC). This study aimed to explore quality of life (QoL) in patients with HNL to guide the development of a patient-reported QoL measure.

Methods: We conducted semi-structured interviews with 22 HNC survivors with HNL. Interviews explored participants' experiences of living with HNL. Analysis of interview transcripts drew on qualitative content analysis to ensure themes were grounded in patient experience.

Results: Two main themes were established: "I want to live my life" and "It was like things were short-circuited." These themes encompassed the substantial disruption patients attributed to the HNL and their desire to normalize life.

Conclusions: Understanding the impact of HNL on individual patients may be critical to optimizing treatment strategies to improve the physical burden of HNL and QoL. This study provides the framework for developing a patient-reported HNL QoL measure.

Implications for cancer survivors: The development of an HNL-specific QoL measure, grounded in the patient perspective, may provide cancer care teams with a tool to better understand HNL's impact on each patient to tailor patient-centered care and optimize QoL outcomes.

Keywords: Head and neck lymphedema, quality of life, head and neck cancer, dysphagia, patient perspective

Background:

Head and neck lymphedema (HNL) is common following treatment for head and neck cancer (HNC), with up to 90% of HNC survivors experiencing some degree of HNL [1-3]. The accumulation of lymphatic fluid in the interstitial spaces may lead survivors to experience compressive symptoms, reduced mobility, and inflammation – all of which may impact the function of surrounding structures [1]. HNL has been associated with speech, swallowing, and breathing difficulties, among other issues [4]. Such functional impairment may limit survivors' participation in many aspects of life and overall well-being [5-6]. Clinical evaluation of patients with HNL often encompasses physical and functional measures; however, the assessment of the emotional impact of HNL is under-represented [7-8].

Quality of life (QoL) is a broad construct related to the subjective perception of well-being. It considers both one’s life conditions and satisfaction with their life conditions, influenced by personal values and expectations [9]. It is increasingly understood that QoL is an important outcome to measure, as it provides balance to purely objective, quantitative measures of health. QoL is particularly relevant given that objective health measures may not correlate with patient perceptions of their health [10-12]. Understanding the patient’s health and well-being perception may influence the treatments and supports offered during recovery.

Previous studies have explored QoL in patients with HNL [5, 13-14]. Nixon and colleagues [5] interviewed ten individuals following treatment for HNL and identified emotional consequences as one main theme, citing issues around identity, appearance, and socialization as major impacts of HNL. A qualitative study conducted by Jeans and colleagues [13] focused specifically on the relationship between HNL and speech/swallow function, identifying a need to remain vigilant in managing the lymphedema to maintain normal speech and swallowing; yet, the direct impact on QoL was not the focus of this study. They did report, however, that most interviewed patients described functional impairments and negative emotional impacts of the lymphedema. McGarvey and colleagues [14] found that while appearance changes associated with HNL were meaningful to women with respect to QoL, male participants expressed greater acceptance of these changes. While these studies provide some insight into patient perspectives of HNL, none sought to ascertain a broad perspective of the impact of HNL on QoL.

Several tools have been described in the literature to measure different aspects of HNL. Two recent systematic reviews [7-8] identified several tools used to describe the severity of HNL and presence of symptoms related to HNL. Both reviews identified the Head and Neck Lymphedema and External Fibrosis Symptom Inventory (HN-LEF) [15] as a well-designed, valid, and reliable tool to measure the presence and severity of patient symptoms. Subscales include soft tissue and neurologic toxicity, systemic symptoms, social functioning, jaw and oral dysfunction, swallowing and taste changes, body image and sexuality, communication, and mucosal irritation. This scale provides valuable information about the types of symptoms a patient experiences due to HNL and the relative severity of such symptoms. Nonetheless, there is currently no extant QoL measure specific to patients with HNL. Some measures exist for measuring QoL in patients with lymphedema of the extremities; however, given the relative visibility of

HNL and its potential impact on identity-defining characteristics (e.g., appearance, speech, and voice), such tools do not adequately assess the perspective of individuals with HNL. As a result, we intend to develop a patient-reported QoL instrument to specifically ascertain the subjective impact of HLN on patients' overall well-being and QoL specific to HNL. This study aimed to explore the lived experience and factors impacting QoL of patients with HNL to guide the future development of an HNL-specific QoL patient-reported outcome measure (PROM).

Methods:

This qualitative study consisted of individual semi-structured interviews completed over a video, web-based platform (Zoom) between June and September 2021. Interviews were structured to explore the lived experiences of individuals with HNL following treatment for HNC as part of a larger effort to develop a patient-reported QoL instrument specific to individuals with HNL. The lead author (HS) conducted the interviews, following an interview guide (Appendix A) developed by the primary investigator with feedback from the study team. A single pilot interview was performed prior to the study interviews to refine the topic guide. Consistent with best practices in qualitative methods, the interview guide evolved over the course of the interviews in response to themes previously identified from prior interviews [16]. While most questions were consistent across interviews, themes raised in early interviews but not fully explored were intentionally addressed in later interviews (e.g., the impact of HNL on intimacy and sexuality). Participants did not have access to the interview guide prior to the interviews. The interviews covered the functional repercussions of HNL across vocational and avocational activities and the social and emotional consequences of living with HNL. Examples of questions include: “What types of problems have you had with the swelling?”; “How has the swelling impacted your daily life and work?”; “Has the swelling prevented you from doing things you would like to do?”; “How has the swelling impacted your self-image?”; and “What concerns do you have for the future if the swelling does not go away?” HS is a clinical speech language pathologist with a Master’s degree and >20 years of experience working with patients treated for HNC. The interviewer had training in qualitative interview methods as part of her doctoral studies. She had an existing clinical relationship with approximately half of the patients interviewed. Interviews lasted 20-60 minutes and were recorded through the Zoom platform and transcribed verbatim into Microsoft Word with patient identifiers removed.

Participants

Individuals diagnosed with HNL by a head and neck clinician were recruited from two international academic medical centers in the United Kingdom (UK) and United States of America (US). Potential participants were referred by HNC practitioners (surgical, radiation, and medical oncologists, as well as speech language pathologists) and invited to participate in person or through email correspondence. Participants were purposively sampled according to demographic factors (age, sex, ethnicity), clinical factors (primary tumor location, cancer treatment, and time post-treatment), and socioeconomic factors. Socioeconomic status (SES) was estimated based on postal code. The Social Deprivation Index [17] was used for participants residing in the United States to characterize socioeconomic status. This index is a composite measure of seven demographic characteristics reported at a zip code level. For participants residing in the UK, the English Indices of Multiple Deprivation [18] and the Welsh Index of Multiple Deprivation [19] were used to estimate SES. To compare between scales, participants were categorized as living in a region in the upper 50% of SES (‘High’) or the lower 50% of SES (‘Low’). All participants provided informed consent prior to participating in interviews as guided by the Stanford Institutional Review Board and the HRA and Healthcare Research Wales ethics boards. They were informed that interviews were being conducted to better understand the patient perspective of living with HNL as part of a larger effort to develop a patient-reported QoL tool. Recruitment ceased when we judged data saturation had been accomplished, and no additional themes were identified. No repeat interviews were performed.

Qualitative analysis

Deidentified transcripts were imported into NVIVO 12 (QSR International Party Ltd, 2019) for qualitative analysis. Each manuscript was reviewed a minimum of three times prior to initiation of coding. Inductive content analysis included initial coding of each transcript followed by secondary, axial coding once all transcripts were coded to explore common themes from the data [16]. Themes were established inductively from the data and were not determined in advance. We selected this analysis approach to ensure themes were grounded in the patient experience, which is particularly important given the overarching goal of developing a PROM. All codes were further stratified into categories and major and minor themes. Coding was performed by the first author, with auditing provided by two authors (BY & MGC), both research psychologists with extensive experience with qualitative methodology, one of whom (MGC) was clinically qualified. The three coders discussed coding discrepancies to establish an agreement.

Ethical approval

The governing research ethics committees of both participating institutions approved the study. Participants were provided with written information regarding the study prior to consent and provided verbal consent prior to interviews. The Standards for Reporting Qualitative Research (SRQR) checklist was utilized [20].

Results

Participants: A total of 22 individuals with HNL were interviewed (Table 1). The average age of participants was 60 years (range 32-78 years), and half were male. Most (77%) participants were White. The most common tumor site was the oral cavity, representing half of those interviewed. Oropharyngeal primaries were noted in 23% of participants (n=5), neck primaries in 10% (n=2), and thyroid, parotid, sinus, and larynx malignancies were each represented by a single participant (5%). Most patients (95%) had surgery and radiation as part of their cancer treatment; fewer had had chemotherapy (36%). Time post-treatment ranged from 2 months to 5 years (mean 15.67 months). Two-thirds (68%) of interviews were conducted with participants from the US. Approximately 60% of participants lived in regions of high SES. Four participants who initially indicated interest in participating did not respond to requests to schedule an interview.

Table 1 Participant characteristics

Part #	Age	Sex	Eth	Tumor Site	Surg	Rad	Chemo	Months post treatment	SES	Country
1	64	F	Hisp	OP	Y	Y	Y	60	High	US
2	53	F	AS	Thyroid	Y	Y	N	6	Low	US
3	61	M	W	OC	Y	Y	N	6	High	US
4	56	F	W	OC	Y	Y	N	12	High	US
5	64	M	W	OC	Y	Y	N	4	Low	US
6	68	F	W	OC	Y	Y	N	12	High	US
7	40	F	AS	Parotid	Y	Y	N	5	High	US
8	70	M	W	Neck	Y	Y	Y	36	Low	US
9	57	M	W	OP	Y	Y	N	24	High	US
10	57	M	W	OC	Y	Y	N	4	High	US
11	78	M	W	OP	N	Y	Y	3	High	US
12	32	M	Hisp	OC	Y	Y	Y	2	High	US
13	59	F	W	Sinus	Y	Y	Y	12	High	US
14	50	F	W	OC	Y	Y	N	6	Low	UK
15	68	F	W	OC	Y	Y	N	18	Low	UK
16	62	F	W	Larynx	Y	Y	Y	8	Low	UK
17	61	M	W	OC	Y	N	N	2	High	UK
18	50	F	AA	OC	Y	Y	N	48	High	US
19	57	M	W	OC	Y	Y	Y	2	Low	UK
20	74	F	W	Neck	Y	Y	Y	48	Low	UK
21	66	M	W	OP	Y	Y	N	13	High	US
22	76	M	W	OP	Y	y	N	30	Low	UK

Key: Part #= Participant number, Surg= surgery, Rad= radiation therapy, Chemo= Chemotherapy, M=male, F=female, Eth=Ethnicity, Hisp= Hispanic, AS=Asian, W=White, AA=African American, OP=oropharynx, OC=oral cavity, Y=yes, N=no, SES=socioeconomic status

Qualitative analysis

HNL appeared to have a broad impact, which varied among participants. Despite these differences, two main themes were established during the analysis: (1) “I want to live my life” and (2) “It was like things were short-circuited.” These themes encompassed the substantial disruption that interviewees attributed to the HNL and the desire to normalize their lives. Within the main theme of "I want to live my life," we identified sub-themes around identity and lifestyle, whereas the main theme of "It was like things were short-circuited" included the subthemes of discomfort and vulnerability. Table 2 provides a categorization of major and sub-themes/codes.

Table 2 Themes, sub-themes, and concepts

Main theme	Sub-theme	Concepts
"I want to live my life"	Identity	Appearance Aging Cancer Survivor
	Lifestyle	Work Relationships Social interactions
"It was like things were short-circuited"	Discomfort	Sensations Function Self-management
	Vulnerability	Lacking knowledge Concern for future/unpredictable Trying to cope

"I want to live my life" Identity: Appearance

Many participants lamented that HNL impacted their internal sense of self and their societal roles in the home, workplace, and social circles. They longed for their normal life in a multitude of ways. For many, the primary struggle was the clearly visible changes in their appearance. This struggle was particularly salient because of the visibility of the head and neck region and the difficulty covering up edema in this region. Participants mentioned avoiding mirrors and photographs due to dissatisfaction with their changed appearance. Female participants consistently reported concerns regarding appearance, which was less of a concern for some male participants.

> *"I don't like my face anymore. I want my face back. …complaining about it feels like vanity. But it's so much more than that. It's about yourself. It's about how you feel about yourself, you know? Your facial expressions are terribly important and very subtle."* (Participant 15)

> *"When you look with disbelief. It's like, I can't believe- is that me? Will I ever look the same, you know?* (Participant 14)

Participants talked of their gratitude for requisite masking due to the coronavirus pandemic, and some were anxious about how they would manage when masking is no longer prevalent. Some participants indicated they would likely continue to mask even when the public health crisis passes as it makes them feel more comfortable around others.

"I want to live my life" Identity: Aging

For a few participants, distress around identity and appearance brought forth concerns about how HNL made them feel and look older than they had prior to cancer diagnosis. Several mentioned that prior to developing lymphedema, they looked younger than their stated age. Interestingly, male participants expressed this concept of premature aging more often. Not only did they express concern about the appearance change, but they also struggled with the sense of vanity they perceived. While the female participants who lamented about appearance changes appeared to be more accepting of their feelings around this change, the male participants appeared to delegitimize their concerns regarding appearance and aging.

> *"And so, the swelling and related topics help and kind of enforce the fact that I'm kind of in a different decade of life. And so that has impact on my confidence- or just projection of my future self. So, it's kind of boiled more into like an aging construct… kind of putting me into a category that I was avoiding."* (Participant 21)

> *"I'm in my 50s and I'm not really young, but I'm also not really old. And so you don't want to have to look, I don't know…older…or worse than you have to if it can be avoided."* (Participant 4)

"I want to live my life" Identity: Cancer survivor

Another important insight from the interviews was how HNL was a constant reminder of the recent struggle with cancer and the new identity of being a cancer survivor. The visibility of HNL and the need for constant management made it impossible for patients to "put the cancer behind them." Participants expressed a sense that they had lost a bit of what they considered their normal lives – replaced by this construct of being a cancer survivor. While in some contexts, being a cancer survivor is akin to being a great warrior, participants viewed this new role as more unwanted and undesirable.

> *“I think, from a psychological point of view it's, it's just a constant reminder that not all is quite right…it just never goes away so it's like something that all day long I'm reminded that there's something significant that I'm dealing with.”* (Participant 2)

“I want to live my life” Lifestyle: Work

In addition to concerns about how changes in appearance impacted one’s sense of identity, participants also expressed how HNL impacted their lifestyle as a whole. For many, this meant adaptation or even avoidance of the workplace due to the lymphedema. For some, this was related to physical limitations, but for many, it was due to wanting to avoid interactions with clients and colleagues due to HNL.

> *“…because a huge part of kind of coming through that was linked to my being able to come back to work. And feeling comfortable and confident around be- I mean my- my job is very much involved with being with the community. And out there, it's not a desk job. So not having something physically limiting or in my appearance was huge to me.”* (Participant 2)

Interestingly, as these interviews took place during the COVID-19 pandemic, the ability to work remotely was cited as a primary reason some participants were comfortable returning to work. However, the ability to maintain physical anonymity in the context of the COVID pandemic is a benefit that not all were privy to. Participants from a lower socioeconomic background appeared to have less opportunity for workplace adaptations and were less likely to have returned to work than their high socioeconomic counterparts.

“I want to live my life” Lifestyle: Relationships

Identity within relationships was another common theme, with many participants discussing how HNL impacted their relationships with close friends and family, more distant and unfamiliar communication partners, and within intimate relationships. Some noted that intimate partners felt emotionally distanced from them due to changes in appearance and difficulty reading non-verbal communication. Frustrations in interactions were commonly cited, with several participants noting that queries about their swelling were annoying. Many just wanted these relationships to return to how they were before developing HNL. Those not in current intimate relationships shared their lack of interest in seeking such relationships, suggesting that the impact of HNL on relationships may span into the future and the present.

> *“My eyes changed a little bit. And my wife would say “I can't read your expressions anymore”.* (Participant 8)

> *“It was the grandchildren. It like scared them a little bit. They have kind of adapted to it because they’ll say to me some days “your face is getting better.” They were a little bit wary of it. But yeah, they are adapting.”* (Participant 19)

> *“I'm single. So, I’m not sure if you want to have that in there- because certainly that affects my…. Even though I'm young, maybe if I had a partner, it would have less effect than right now given that I’m single, so...* (regarding dating) *And right now, there’s no interest. Not- maybe not NO interest, but I just don’t want to do that.”* (Participant 12).

“I want to live my life” Lifestyle: Social interactions

Social interactions were similarly impacted by HNL and spanned from avoiding situations/interactions with unfamiliar individuals to avoidance of all social interactions. The disruptions in social interactions were related to changes in functions such as speech and eating and to reticence to allow others to see them in the new context of being a cancer survivor. Additionally, several participants also mentioned that their HNL negatively impacted their stamina and tolerance for social situations. These issues were reportedly related to sensory issues and fatigue with maintaining focus on trying to cover up the lymphedema (e.g., trying to keep the more swollen side out of view of others). The efforts required for such social activities overcame the value of being a part of the activities, leading to disengagement in socialization. Overall, participants were less likely to engage in social activities and expressed less enjoyment when participating, particularly younger individuals and those who were single.

“I haven't been out um socially. Just because how it looks basically.” (Participant 17)

> *“I'm able to go out and do what I want to do, it's just the length of time that I'm able to sustain it…not being able to last. Or kind of the, the pain getting overwhelming.”* (Participant 2)

“It was like things were short-circuited” Discomfort

In addition to the changes in identity, many participants had a sense of their physical and emotional equilibrium being “short-circuited.” They did not feel that they were able to maintain their habitual homeostasis. This feeling manifested as physical discomfort and dysfunction, as well as a sense of vulnerability to change and the uncertain future. As appearance was a major contributor to the identity theme, the physical impacts of HNL contributed greatly to this sense of being derailed. Many participants cited disturbing sensory changes such as tightness and fullness that were ever-present. Such physical sensations directly impacted functions such as eating, speaking, and sleeping.

> *“I can feel quite claustrophobic with it because I literally feel like I had a rope tied around my neck.”* (Participant 14)

> *“…Like I’ve been to the dentist in a way. Like when they stuff your face with cotton balls- it just feels just pushed out. Almost like my tongue is thick and heavy.”* (Participant 18)

“It was like things were short-circuited” Self-management

Some cited self-management of the HNL as a challenging burden. For some, this was related to difficulties with the technical aspects of the treatment, while for others, it was the logistics of integrating this into their otherwise “normal” life. Some participants had caregivers who assisted with the lymphedema management; some cited this as a nice way to connect with their loved ones. Others felt empowered for the first time in their cancer journey to enhance their overall health and well-being. The self-management process brought very different impacts to participants depending upon their circumstances and outlook on treatment.

> *"And it's very difficult anyway to be remotely as efficient as a trained lymphedema nurse who can do it from a different angle and is professional and knows exactly what they're doing. Even with lots of practice, you're still a layperson trying to do it on your own body, which is difficult."* (Participant 15)

> *"The problem with cancer is that you're not in control. I'm not in control of the radiation. I'm not in control of the chemo. Right? I mean, I can do that, you know that, the swallowing exercises. I can do all that kind of stuff, but really, it's out of my control. And so, this feels like a little bit more like okay, well, I'm doing something about this."* (Participant 11)

"It was like things were short-circuited" Function

A multitude of functional challenges were also attributed to HNL. The majority of participants reported an impact on eating and swallowing, frequently resulting in the need to adapt the types of foods consumed. There was also fear of food getting stuck and choking when swelling was more severe. Several participants reported a direct relationship between their swelling and speech/voice, indicating that they would avoid conversations and interactions when more swollen. Other functional issues included challenges with driving, breathing, and sleeping. Several individuals reported needing to sleep out of the bedroom in a more upright position to assist with breathing and sleeping. Less frequently, participants mentioned issues such as difficulties with sight and hearing when swelling increased. Other physical limitations were reported, such as the inability to wear certain items like jewelry and bike helmets, difficulty shaving, and whistling. These functional issues together created a sense of inability to live a normal life.

> *“How important is it to move your head? Well, it's really important every time you back out of the driveway, and you need to look both ways to find out if you're rolling over a little kid on the sidewalk.”* (Participant 9)

> *“You try to sleep sitting up a little bit to try and keep it draining. Because at first, I was lying down because I was so exhausted. But then I would wake up, and it would be super swollen and stiff because the fluid’s not able to go anywhere. So you’re just constantly like, you know, waking every hour, really.”* (Participant 14)

> *“So if I'm trying to put makeup on … well, if I'm putting makeup on, it takes me much longer, because my I've got two different eyes. And eyelids. And that's really quite tricky to do. And my face shape isn't… it’s wrong, so anything that you use is- you've got to do it differently on one side to the other and keep trying to sort of adjust it. And at the at the end, when I’ve done it, I think, well, you can't make a silk purse out of a sow's ear. I never look at myself and think, “Yeah, you look nice.” Never. So, I never go out feeling confident.”* (Participant 15)

“It was like things were short-circuited” Vulnerability

The interplay of all these issues leads to a sense of vulnerability in many participants – both in the present and in concerns for the future. Participants described attempts to cope with their changed circumstances, with some willing to accept these changes more than others. Negative feelings about the lymphedema were common, such as sadness, regret, anger, and frustration. Similarly, the lack of predictability around the swelling raised anxiety and concern. With HNL, there is uncertainty about the potential for improvement and the future impact of the condition. For some, this also raised questions about whether the cancer had been fully treated. This uncertainty led to feelings of vulnerability, need for knowledge, and anxiety. Broadly, there was a sense of need for vigilance regarding the lymphedema.

> *“Well, when I first saw it, I didn't know what it was. And you know, whenever you have cancer and you something appears and you don’t know what it is, your natural reaction is “this is not good.”* (Participant 11)
>
> *“But the lymphedema is… just- I'm just angry. I'm fuming. I'll never be anything less than angry about it unless something comes along that can get rid of it for me.”* (Participant 15)
>
> *“I still do get depressed because I want to be a normal person, which that will never happen again.”* (Participant 1)
>
> *“And I think the thing that comes across the most is the, the feeling of helplessness. And sort of the idea that your own body is turning against you.*

That's a little scary you don't want- you don't want to consider that." (Participant 11)

Discussion:

Bury (1982) [21] once described chronic illness as a "biographical disruption." Based on the interviews conducted, we would assert that cancer diagnosis, treatment, and survivorship similarly act as a significant biographical disruption. HNL crosses the boundaries between the acute cancer treatment phase and the world of chronic conditions, often requiring lifelong management. Thus, patients with HNL experience both the biographical disruption of the cancer diagnosis and the longer-term disruption from changes in appearance and function.

Consistent with other studies of patients with HNL [1, 5, 14], physical, emotional, and functional ramifications of HNL were evident in all participants. As would be expected, the intensity of the impact of these changes varied among participants; however, some commonalities were observed across the sample. As previously discussed, one main theme identified from the data was "I want to live my life." This primary theme of adapting to changes in identity and appearance is similar to reports by Nixon and colleagues [5]. In contrast to McGarvey's work [14], which highlighted appearance as the main impact of HNL, our participants identified multiple functional impacts of HNL that impacted their ability to live as they did before being diagnosed with HNC. Changed identity was not solely related to appearance but also an increased sense of vulnerability, changed social roles, premature aging, and living as a cancer survivor. These changes in self-perception had a clear impact on role definitions and social engagement. For many participants, this impact also resulted in significant changes in their ability to return to work, raising concerns for a population already at risk for financial toxicity [22-23].

In addition to changes in patients' perceptions of their identity, many participants discussed at length how their day-to-day life changed, as exemplified by the statement, "It was like things were short-circuited." Participants discussed physical discomfort and its impact on task performance and endurance. Nixon and colleagues [5] described this as their major theme of "day-to-day distress." In our report, as with theirs, these impacts spanned multiple domains including eating, speaking, driving, sleeping, and general movement of the head and neck region. This finding is an important contrast from the perspective of head and neck clinicians in the McGarvey study, who minimized the potential functional implications of HNL and highlights the need for clinicians to improve awareness of the functional impact of HNL [14]. In several cases, participants mentioned that, at times, their symptoms were so great that they would just go to bed to avoid having to deal with them. The emotional impact of these challenges varied widely. It ranged from acceptance of the "new normal" to a sense of despair, highlighting the importance of measuring QoL impacts, not merely the presence of symptoms.

An extensive body of literature exists regarding the impact of lymphedema on QoL. Patients with gynecologic and breast cancers with lymphedema have reported decrements in aspects of QoL including physical limitations, emotional challenges, and social/vocational difficulties with lower QoL associated with greater symptom burden [24-25]. While similarities exist between patients with HNL and other forms of lymphedema with respect to QoL impact, it became clear through these interviews that the impact of HNL on patients and QoL is significant and unique to those with HNL. While the Lymphedema Quality of Life Inventory (LyQLI) [26] includes several of the concepts that arose during these interviews, it does not address issues such as eating and speaking, which are significant drivers of QoL in the HNC population [27-29]. More than half of our participants cited eating and talking as significantly impacted by HNL. Thus, it appears important to consider such constructs when examining QoL in patients with HNL.

While there is often a relationship between symptoms and QoL, these constructs may also diverge. The lack of direct concordance between symptom severity and QoL may be related to psychological resilience [30], coping mechanisms [31], sense of coherence [31-32], and self-compassion/hope [33]. According to Wilson and Cleary (1995) [34], "general measures of life satisfaction or happiness are not as strongly related to objective life circumstances as might be anticipated, lower levels of function are not necessarily related to lower levels of satisfaction." For example, while Participant 3 cited substantial symptoms with eating and talking, when queried about the impact on his emotional state, he expressed a sense of acceptance stating, "You know, it wasn't playing with my mind. It's just like, "Okay, this is what happens." While existing scales such as the Head and Neck Lymphedema and External Fibrosis Symptom Inventory [15] capture the presence and severity of symptoms related to HNL, which may provide some insight into patient perception of symptoms, there is no extant scale to capture the impact of such symptoms on an individual's broader QoL. Based upon the known potential for variance between symptoms and QoL, creating a tool specifically examining QoL in patients with HNL is important to discern the types of treatment required for each patient and to track the impact of treatments on a patient's sense of well-being. While some concerns may exist regarding the time required to complete such surveys in the clinic, there is evidence that a Patient Concerns Inventory approach can yield beneficial information without adding excessive time to the clinical encounter [35]. By identifying a patient's specific concerns, clinicians will be able to identify the most appropriate types of treatment, which may include speech and swallowing therapy, psychological counseling, or vocational interventions. Personalizing interventions to a patient's specific concerns may result in more cost-effective, efficient care [36].

The voices and perspectives of patients are critical in developing any PROM. In this study, the physical, functional, and emotional experiences of individuals with HNL were explored qualitatively, with the future goal of developing a patient-reported QoL instrument specific to HNL. These interviews provided insight into the challenges these individuals experienced and their strategies to overcome them, providing important context as we embark on item generation for PROM development.

As with any study, there are limitations to this work. Despite the use of purposive sampling, our participants were predominantly White. While the percentage of White participants is similar to distributions in the US and UK and reflective of head and neck cancer patients [37-38], it is possible that this sample may have underrepresented themes important to other ethnic groups. It is also important to acknowledge that these interviews were conducted during the acute phase of the COVID-19 pandemic. The forced changes to social interactions during this period may have influenced how some of these participants viewed the impact of their HNL. Interestingly, many participants indicated that required mask wearing was a positive thing for them, and they worried about a time when mask wearing would be less prevalent. Another potential limitation is that some participants had an existing relationship with the interviewer, which may have influenced how they responded to some questions. While this is a potential limitation, we found that participants were quite forthcoming regardless of their previous relationship with the interviewer. A final important consideration is that participants may have difficulty discerning between the impact of HNL and other treatment-related side effects. While questions were posed to focus specifically on the impact of HNL, some of the reported impacts may be related to other treatment toxicities.

This study provides the patient-perspective framework for developing a patient-reported HNL QoL instrument. We explored the experiences of a broad population of individuals with HNL to guide item generation for this tool. Future work will include item generation and refinement, with input from both patients and experts. The draft instrument will then be pilot tested with cognitive interviewing strategies prior to formal validation testing.

Conclusions:

As evidenced by this study, head and neck lymphedema can impact patients in many ways and to varying degrees. These insights provide our team with critical perspectives to consider during our ongoing development of a QoL measure. Understanding the QoL impact of HNL on an individual patient may be critical to optimizing treatment strategies to improve the physical burden of lymphedema and its impact on QoL. These interviews highlighted the physical ramifications of HNL and the psychological sequela of living with HNL. This study provides the framework for developing a patient-reported QoL instrument specific to the needs of cancer survivors with HNL.

References:

1. Deng J, Murphy BA, Dietrich MS, et al. Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. *Head Neck*. 2013;35(7):1026-1035. doi:10.1002/hed.23084
2. Jackson LK, Ridner SH, Deng J, et al. (2016). Internal lymphedema correlates with subjective and objective measures of dysphagia in head and neck cancer patients. Journal of Palliative Medicine, 19(9): 949-56.
3. Ridner SH, Dietrich MS, Niermann K, et al. (2016). A prospective study of the lymphedema and fibrosis continuum in patients with head and neck cancer. Lymphatics Research and Biology, 14(4): 198-205.
4. Deng J, Murphy BA, Dietrich MS, Sinard RJ, Mannion K, Ridner SH. Differences of symptoms in head and neck cancer patients with and without lymphedema. *Support Care Cancer*. 2016;24(3):1305-1316. doi:10.1007/s00520-015-2893-4
5. Nixon JL, Pigott AE, Cartmill B, Turner J, Fleming J, Porceddu SV. A mixed methods examination of distress and person-centred experience of head and neck lymphedema. *Oral Oncol*. 2018; 83:18-24. doi:10.1016/j.oraloncology.2018.05.025
6. Ringash J, Bernstein LJ, Devins G, et al. Head and Neck Cancer Survivorship: Learning the Needs, Meeting the Needs. *Semin Radiat Oncol*. 2018;28(1):64-74. doi:10.1016/j.semradonc.2017.08.008
7. Starmer H, Cherry MG, Patterson J, Young B, Fleming J. Assessment of Measures of Head and Neck Lymphedema Following Head and Neck Cancer Treatment: A Systematic Review [published online ahead of print, 2022 Jun 9]. *Lymphat Res Biol*. 2022;10.1089/lrb.2021.0100. doi:10.1089/lrb.2021.0100

8. Fadhil M, Singh R, Havas T, Jacobson I. Systematic review of head and neck lymphedema assessment [published online ahead of print, 2022 Jul 11]. *Head Neck*. 2022;10.1002/hed.27136. doi:10.1002/hed.27136
9. Felce D, Perry J. Quality of life: its definition and measurement. *Res Dev Disabil*. 1995;16(1):51-74. doi:10.1016/0891-4222(94)00028-8
10. Kendall KA, Kosek SR, Tanner K. Quality-of-life scores compared to objective measures of swallowing after oropharyngeal chemoradiation. Laryngoscope. 2014;124(3):682–7.
11. Pedersen A, et al. Swallowing outcome measures in head and neck cancer: how do they compare? Oral Oncol. 2016; 52:104–8.
12. Arrese LC, Carrau R, Plowman EK. Relationship between the Eating Assessment Tool-10 and objective clinical ratings of swallowing function in individuals with head and neck cancer. Dysphagia. 2017;32(1):83–9.
13. Jeans C, Ward EC, Cartmill B, et al. Patient perceptions of living with head and neck lymphedema and the impacts to swallowing, voice and speech function. *Eur J Cancer Care (Engl)*. 2019;28(1): e12894. doi:10.1111/ecc.12894
14. McGarvey AC, Osmotherly PG, Hoffman GR, Chiarelli PE. Lymphedema following treatment for head and neck cancer: impact on patients, and beliefs of health professionals. *Eur J Cancer Care (Engl)*. 2014;23(3):317-327. doi:10.1111/ecc.12134
15. Deng J, Dietrich MS, Niermann KJ, et al. Refinement and Validation of the Head and Neck Lymphedema and Fibrosis Symptom Inventory. *Int J Radiat Oncol Biol Phys*. 2021;109(3):747-755. doi:10.1016/j.ijrobp.2020.10.

16. Braun V & Clarke V. (2013). Successful Qualitative Research: A Practical Guide for Beginners. Sage Publishing. Thousand Oaks, CA.
17. Robert Graham Center. Social Deprivation Index (SDI). 2018.
18. English Indices of Deprivation 2019. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019. Accessed September 16, 2022.
19. Welsh Index of Multiple Deprivation, 2020. https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation. Accessed September 16, 2022.
20. O'Brien, Bridget C. PhD; Harris, Ilene B. PhD; Beckman, Thomas J. MD; Reed, Darcy A. MD, MPH; Cook, David A. MD, MHPE. Standards for Reporting Qualitative Research: A Synthesis of Recommendations. Academic Medicine: September 2014 - Volume 89 - Issue 9 - p 1245-1251 doi: 10.1097/ACM.0000000000000388
21. Bury M. Chronic illness as biographical disruption. *Sociol Health Illn*. 1982;4(2):167-182. doi:10.1111/1467-9566.ep11339939
22. Mady LJ, Lyu L, Owoc MS, et al. Understanding financial toxicity in head and neck cancer survivors. *Oral Oncol*. 2019; 95:187-193. doi:10.1016/j.oraloncology.2019.06.023
23. Beeler WH, Bellile EL, Casper KA, et al. Patient-reported financial toxicity and adverse medical consequences in head and neck cancer. *Oral Oncol*. 2020; 101:104521. doi:10.1016/j.oraloncology.2019.104521
24. Bowman C, Piedalue KA, Baydoun M, Carlson LE. The Quality of Life and Psychosocial Implications of Cancer-Related Lower-Extremity Lymphedema: A

Systematic Review of the Literature. *J Clin Med*. 2020;9(10):3200. Published 2020 Oct 2. doi:10.3390/jcm9103200

25. Pusic AL, Cemal Y, Albornoz C, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. *J Cancer Surviv*. 2013;7(1):83-92. doi:10.1007/s11764-012-0247-5
26. Klernäs P, Johnsson A, Horstmann V, Kristjanson LJ, Johansson K. Lymphedema Quality of Life Inventory (LyQLI)-Development and investigation of validity and reliability. *Qual Life Res*. 2015;24(2):427-439. doi:10.1007/s11136-014-0783-8
27. Nayak SG, Pai MS, George LS. Quality of life of patients with head and neck cancer: A mixed method study. *J Cancer Res Ther*. 2019;15(3):638-644. doi:10.4103/jcrt.JCRT_1123_16
28. Arslan HH, Ahmadov A, Cebeci S, Binar M, Karahatay S. Life Priorities in Head and Neck Cancer Patients Between Ages of 45 to 65. *J Craniofac Surg*. 2016;27(4): e398-e401. doi:10.1097/SCS.0000000000002671
29. Fingeret MC, Hutcheson KA, Jensen K, Yuan Y, Urbauer D, Lewin JS. Associations among speech, eating, and body image concerns for surgical patients with head and neck cancer. *Head Neck*. 2013;35(3):354-360. doi:10.1002/hed.22980
30. Mace RA, Doorley J, Bakhshaie J, Cohen JE, Vranceanu AM. Psychological resiliency explains the relationship between emotional distress and quality of life in neurofibromatosis. *J Neurooncol*. 2021;155(2):125-132. doi:10.1007/s11060-021-03852-1

31. Ngai FW. Relationships between menopausal symptoms, sense of coherence, coping strategies, and quality of life. *Menopause*. 2019;26(7):758-764. doi:10.1097/GME.0000000000001299
32. Asaba K, Okawa A. Moderating effect of sense of coherence on the relationship between symptom distress and health-related quality of life in patients receiving cancer chemotherapy. *Support Care Cancer*. 2021;29(8):4651-4662. doi:10.1007/s00520-021-06003-4
33. Klein DE, Winterowd CL, Ehrhardt MD, Carter JC, Khan O, Mayes S. The relationship of self-compassion and hope with quality of life for individuals with bleeding disorders. *Haemophilia*. 2020;26(3): e66-e73. doi:10.1111/hae.13959
34. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA*. 1995;273(1):59-65.
35. Rogers SN, Semple C, Humphris GM, Lowe D, Kanatas A. Using a patient prompt list to raise concerns in oncology clinics does not necessarily lead to longer consultations. *Br J Oral Maxillofac Surg*. 2020;58(9):1164-1171. doi:10.1016/j.bjoms.2020.08.035
36. Ezeofor V, Spencer LH, Rogers SN, et al. An Economic Evaluation Supported by Qualitative Data About the Patient Concerns Inventory (PCI) versus Standard Treatment Pathway in the Management of Patients with Head and Neck Cancer. *Pharmacoecon Open*. 2022;6(3):389-403. doi:10.1007/s41669-021-00320-4
37. Du XL, Liu CC. Racial/Ethnic disparities in socioeconomic status, diagnosis, treatment and survival among Medicare-insured men and women with head and

neck cancer. *J Health Care Poor Underserved*. 2010;21(3):913-930. doi:10.1353/hpu.0.0331

38. Delon, C., Brown, K.F., Payne, N.W.S. *et al.* Differences in cancer incidence by broad ethnic group in England, 2013–2017. *Br J Cancer* 126, 1765–1773 (2022). https://doi.org/10.1038/s41416-022-01718-5

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Data availability: The deidentified datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Interview questions

Tell me a little about the kind of treatment you went through for your cancer.

How long has it been since you went through cancer treatment?

How are you feeling today?

What are some of the challenges you have encountered?

What has helped you the most in your recovery?

Tell me about when you first noticed swelling around your neck or face?

Was the swelling something you had heard about before you noticed it?

What were your thoughts and concerns about it initially? Has that changed with time?

How does the swelling feel?

What types of problems have you had with the swelling?

How has the lymphedema impacted you?

Your daily life or work?

Your family?

Your relationships?

Your functioning in things like speaking and swallowing or breathing?

What is a bad day like with the swelling? How about a good day?

Have other people noticed or commented on the swelling?

Has the swelling prevented you from doing things you would like to do?

If we could make the swelling disappear completely, what do you think might be different for you?

Our experiences with our health are not always physical. How did the swelling impact you from a mood perspective?

Have you met with a specialist about your swelling?

(If yes) Tell me about your initial contact with the lymphedema team.

How did you feel after that meeting?

What were your initial thoughts about lymphedema therapy?

How did those thoughts change over time?

What aspects of that intervention were helpful? What went better than expected? What went worse than expected?

How do you feel the therapy helped you?

What kinds of challenges did you encounter with the therapy?

(If no) What kind of support do you think would be helpful for you in regard to the swelling?

How do you feel about lymphedema now?

What kinds of concerns do you have for the future in regard to the swelling?

What ideas or suggestions do you have for improving therapy/support for patients like yourself?

7. Development of an HNL HRQoL PROM (Published paper)

7.1. Study rationale

The systematic review presented in Chapter 3 identified that there is not currently an instrument available that measures all domains of HNL-specific HRQoL. The qualitative interviews presented in Chapter 6 demonstrated HNL may affect HRQoL in numerous ways, including physical appearance and sensations, functional participation in personal and vocational activities, and emotional outcomes. Understanding these impacts at an individual level may impact clinical management, as discussed in Chapter 5. Because of the substantial impacts on HRQoL reported by patients with HNL during these qualitative interviews, and in prior publications (Deng et al., 2019; Deng, Murphy, et al., 2015; Jeans et al., 2019), I identified that there was a gap between patient perceptions/experiences and the tools available to measure them. Hence, I decided that developing an HNL-specific HRQoL PROM would be a valuable effort for this thesis. This was validated by discussions with clinician experts who indicated that such a tool would be beneficial in their clinical practice as well as for future research endeavors.

7.2. Comments on patient-reported outcome measure development

One important consideration when developing a new PROM is determining the intended purpose of the tool. PROMs initially gained popularity for research purposes to measure treatment effects, however, have expanded use into clinical decision making and quality assurance work (Churruca et al., 2021). Based on my clinical experience as a lymphoedema rehabilitation specialist and my role as a clinical researcher, the genesis of this project was the need to determine the impact of lymphoedema interventions both for clinical and research purposes. Thus, the primary intent of this PROM was to determine change in HNL-related HRQoL in response to treatment. Secondarily, I hoped that this tool could also serve as a conversation starter in clinical settings so that clinicians could have a better understanding of the ways in which HNL is impacting a particular patient to drive patient-centred care.

One of the most challenging aspects I experienced during PROM development was maintaining a balance between comprehensiveness and succinctness. The qualitative interviews in Chapter 6 identified a myriad of issues that patients with HNL might experience. To ensure this PROM would be practical for use in clinical and research applications, it was necessary to distill these numerous concerns into more broadly representative items. I felt a real sense of obligation to ensure the patients' voices were reflected in the items developed, but also a need for the items to be more universal so that the PROM was not unwieldy. At the same time, clinicians indicated the need for a very succinct instrument, some indicating that more than 10 items would be too burdensome. In contrast to the clinicians' perspectives, patient participants felt it was important not to cut too many items from the instrument so that it would be broadly representative. These conflicting opinions weighed heavily on all decisions made during item reduction. It was reassuring during the three-step interviews described in the manuscript below that patients indicated that the length of the instrument was not excessive and that they would be willing to complete such a survey as part of their clinical care. This validated, for me, that the extra items likely bring value, at least from a patient perspective.

From a clinician's perspective, I also understand that increased specificity in a PROM provides the clinician with more actionable information. Thus, given the importance of a patient-centered approach to HRQoL measurement, I weighed the feedback of the patients as more important than that of the clinicians regarding instrument length. Importantly there is precedence for this decision, as other investigators have found patients willing to complete more lengthy PROMs if they believed this would impact their care (Atkinson et al., 2019). Although the primary intent of this PROM is to measure change over time or in response to treatment, I also hoped it would serve the need of helping to identify patient concerns that could be acted upon in a clinical setting.

During PROM construction, I had the opportunity to speak with Dr. Barbara Murphy, one of the lead developers of the HN-LEF Symptom Inventory. We talked about the constructs captured by the HN-LEF Symptom Inventory and the relative lack of consideration of social and emotional impacts on that scale. This communication confirmed the need to be very mindful about including a variety of psychosocial impacts of HNL as identified in the qualitative interviews. Many of the probing questions asked during the three-step interviews involved the items within the emotional domain, to ensure comprehensive coverage of this domain.

Response format and scoring are other important considerations during PROM development. My prior experience with a variety of PROMs made me sensitive to issues I have seen regarding these aspects of PROMs. For example, the MD Anderson Dysphagia Inventory (MDADI) has two items that are scored in an inverse fashion to the other items (Chen et al., 2001). In practice, many patients respond incorrectly, likely related to difficulty understanding the items and a bias towards responding in a similar manner across instrument items (Toft, et al., 2024). As outlined in Chapter 5, I wanted to avoid inverse scoring, negatively phrased questions, and complex language to improve the accuracy of patient reports as well as to reduce the potential for missing data (Peasgood et al., 2021). Another aspect of the MDADI which I have found to be problematic is the wording of the response options, ranging from “strongly agree” to “strongly disagree”. Many individuals I have encountered feel that some of the items on the MDADI do not apply to them (e.g. “My swallowing difficulty has caused me to lose income”). As a result, they don’t feel any of the response options are appropriate. Therefore, it is not uncommon for individuals to write “n/a” alongside such items. This raises concerns about how to interpret scores in the context of missing data. As a result of such experiences, scale response option wording was an important part of the three-step interviews, to ensure that participants felt they could respond to each item. Thus, the frequency of occurrence of symptoms was selected for this instrument rather than the severity of symptoms.

One challenging decision regarding the publication of the instrument under development, the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN), (Figure 7-1) was whether to include the entire scale in the publication. While I recognised that reviewers and readers would want to be able to access and review the instrument, I decided that I would not publish it prior to further validation and field testing. By not publishing the pilot instrument, I decrease the risk that the CALI-HaN will be inappropriately implemented prior to establishing validity and reliability.

Figure 7-1 The Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN)

Lymphedema is a type of swelling that is common after treatment for head and neck cancers.

Quality of life refers to your overall sense of well-being.

Please answer the following questions thinking about how your lymphedema has impacted your quality of life on average over the past 7 days. We understand you may have other symptoms you are dealing with, but for this purpose of this survey, please try to respond specific to the impact of lymphedema.

	Never	Infrequently	Sometimes	Frequently	Always
1. Lymphedema had an impact on my quality of life.					
Because of lymphedema…					
2. Moving my head and neck was painful.					
3. My eating/swallowing was difficult.					
4. My ability to work or do my daily activities was impacted.					
5. I avoided certain foods.					
6. I did not like the way I look.					

7. My speech was unclear.					
8. It was difficult to open my mouth.					
9. I did not feel well-rested.					
10. When I woke up in the morning it was hard to move.					
11. It was hard to breathe.					
12. I was unhappy.					
13. My sexual or intimate activities were affected.					
14. It was difficult to see clearly.					
15. I tended to avoid social activities.					
	Never	**Infrequently**	**Sometimes**	**Frequently**	**Always**
16. I was concerned that my cancer would come back.					
17. It was difficult to drive.					
18. My voice did not sound normal.					
19. People had difficulty understanding me when I was swollen.					
20. I felt anxious.					
21. I did not sleep well.					
22. I felt more negatively about myself.					
23. I felt less comfortable in social situations.					
24. I was concerned that lymphedema may cause other health issues in the future.					
25. I was embarrassed by lymphedema.					
26. I was frustrated by lymphedema.					
27. I felt like I needed to hide lymphedema from others.					
28. It bothered me how visible my lymphedema is.					
29. I was concerned about how lymphedema impacts things like eating, talking, and breathing.					
30. I felt like I had no control over lymphedema.					

31. I was always aware of lymphedema.					
32. I did not know how lymphedema would be from day to day.					
33. I was concerned about lymphedema getting worse in the future.					

7.3. Presentation and publication

7.3.1. Presentation

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7.3.2. Publication

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7.4. Contributions

Heather Starmer conceived and designed the study, generated initial items from qualitative interviews, developed and analysed data from the Qualtrics survey, lead the binning and winnowing process, revised the survey items and drafted the manuscript under the supervision of Joanne Patterson, Jason Fleming, Gemma Cherry, and Bridget Young. Joanne Patterson, Gemma Cherry, Bridget Young, and Jason Fleming all participated in the binning and winnowing process. Substantive feedback regarding the three-step interviews and analysis of interview data was provided by Gemma Cherry and Bridget Young. All authors contributed to development of the manuscript and approved the final article.

7.5. Published study:

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Development of a head and neck lymphoedema specific quality of life tool: The Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN)

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Running heading: Development of a head and neck lymphoedema specific quality of life tool

Keywords: lymphedema, lymphoedema, head and neck lymphedema, quality of life

Abstract:
Purpose: To develop a head and neck lymphoedema (HNL) specific quality of life (QoL) instrument to assess physical, functional, and social/emotional impacts of HNL.

Methods: Instrument candidate items were reviewed by HNL patients and clinicians and rated for importance, clarity, and invasiveness. The Content Validity Ratio was applied for item reduction. Three-step cognitive interviews were conducted with HNL patients to validate the items, survey format, and instructions.

Results: Initially, 130 candidate questions were developed. Following item reduction, 52 items progressed to three-step cognitive interviews. Following cognitive interviews, the Comprehensive Assessment of Lymphoedema Impact in Head and Neck (CALI-HaN) included 33 items: one global, ten physical, seven functional, and fifteen emotional.

Conclusions: Physical, functional, and socioemotional effects need to be considered when measuring QoL in patients with HNL. This study describes initial development of the CALI-HaN, an instrument that shows promise for clinical and research applications following future validation.

1. Background:

Head and neck lymphoedema (HNL) is a common, unintended consequence of head and neck cancer (HNC) and its treatments, with prevalence rates up to 90% following HNC treatment [1-2]. HNL occurs when the lymphatic system is injured, leading to accumulation of lymph fluid in the interstitial spaces. Physical and anatomic changes due to inflammation, compression, reduced mobility, and fibrosis resulting from HNL may lead to functional impairment, such as dysphagia and dysphonia [3-4]. As a result of these functional impairments, individuals with HNL may have reduced satisfaction in their quality of life (QoL) [5-6].

Health related quality of life (HRQoL) refers to “a state of complete physical, mental, and social well-being and not merely the absence of disease” [7]. Assessment of HRQoL therefore needs to encompass not only physical functioning, but also emotional and social well-being. A recent systematic review of patient reported outcomes measures (PROMs) used for patients with lymphoedema identified 17 lymphoedema-specific QoL measures, the majority of which were developed for patients with limb lymphoedema [8]. Only one scale was developed for those with HNL. The overall methodologic quality for instrument development was low to moderate, citing a lack of patient involvement as a major shortcoming of most of the instruments reviewed, including the instrument designed for HNL. Based on their review, they advocated for the development of PROMs for patients with lymphedema, using a more patient-centric approach.

It is well established that individuals diagnosed with HNC are at risk for both short and long-term decrements to QoL [9-10]. Further, there appears to be a relationship between poorer QoL and higher rates of depression and anxiety [11-13]. It has been shown that patients with more severe HNL have more functional impairment and poorer QoL [3]. It is important then that clinicians and researchers interested in the impact HNL treatments are able to assess not just the physical and functional effects of treatment, but also the socioemotional impacts of treatment. PROMs are considered to be the gold standard for assessing subjective patient perspectives [14]. To date, there is no tool developed specifically to encompass all aspects of QoL related to HNL.

The Patient Reported Outcomes Measurement Information System (PROMIS) recommends a 5-step process for development of PROMs [15]. Following a systematic review of existing measures, qualitative interviews and/or focus groups should be completed to identify concepts important to patients with a specific condition. Thematic analysis is then performed to identify themes common to individuals with the condition to guide development of the initial item bank. Once this item bank is developed, additional cognitive interviews should be performed with individuals with the target condition to validate the item bank prior to psychometric field testing. The COSMIN study design checklist provides additional guidance for designing a study regarding measurement tools such as PROMs [16].

Given the unique functions of the head and neck region in respect to appearance, communication, intimacy, and consumption of food and liquid, it is imperative that these issues are addressed in any specific PROM used to measure QoL in patients with HNL. The 64-item Lymphedema Symptom Intensity and Distress

Survey – Head & Neck (LSIDS-HN) was initially designed to characterize the symptom burden specific to those with HNL and fibrosis [17-18]. Patients are asked to indicate the level of "intensity" as well as "distress" associated with each symptom, using two separate 5- point Likert scales. During validation testing, the test length was raised as a concern by ~60% of those studied. Further, they reported a high level of agreement between intensity and distress ratings, suggesting that patients did not consider these to be separate constructs. Thus, the authors removed the "distress" response option and shortened the symptom list to 33 items, renaming the instrument the Head and Neck Lymphedema and Fibrosis Symptom Inventory (HN-LEF Symptom Inventory) [19]. Of the 33 items retained, most (28) refer to physical and functional symptoms with few items related to emotional well-being.

While the HN-LEF Symptom Inventory is a valuable tool for understanding symptom burden, there remains a need for a QoL instrument that will also capture the social and emotional consequences of HNL. As a result, the purpose of this study was to develop an HNL-specific QoL instrument to assess physical, functional, and social/emotional domains. We have previously reported the results of our systematic review and qualitative interviews conducted in early stages of scale development [20-21]. This paper outlines the development process from item generation through cognitive interviewing for the creation of the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN).

2. Methods:

Phase 1: Item generation

Item generation for a patient-reported QoL instrument includes consideration of extant scales and interrogation of the patient perspective. A systematic review was performed to identify extant tools which were examined to identify possible constructs and relevant items for consideration [20]. Qualitative interviews were conducted with 22 HNC patients from the UK and US with lymphoedema [21]. As previously published, the average age of participants was 60 years, 50% were male, and 77% were white. 50% of participants had oral cavity primaries and the overwhelming majority (95%) had a combination of surgery and radiation (demographics of this sample can be found in Table 1). Based on these interviews, candidate items were generated to reflect key themes. Items were generated by the first author and reviewed by the study team to ensure concordance with the findings of the qualitative interviews. Binning and winnowing were conducted by the study team once the initial items were generated. Binning refers to a systematic process of grouping items according to meaning to identify redundancy and completeness of encapsulating the construct(s) of interest. Winnowing is the process of eliminating those items judged to be redundant or inadequate for the purpose of the instrument being developed [15].

Phase 2: Initial validation and item reduction

Patients with HNL and HNC practitioners (n=18) were invited to participate in a study to examine the clarity, importance, and intrusiveness of the candidate items. Inclusion criteria for patients were; a prior diagnosis of HNC and HNL, age>18, English proficiency, and ability to access an online survey instrument. Clinicians were experienced in working with patients with HNC and HNL. Specialties invited to participate included surgical, radiation, and medical oncologists, nurses, physiotherapists, occupational therapists, and speech-language therapists. Ethics board approval was granted for all phases of this study.

A Qualtrics survey (Qualtrics, Provo UT) was developed and included each candidate item. Patient and clinician participants were asked “How important is this item?” using a 4-point Likert scale (1= not important and 4=very important). Additionally, they were asked “How easy is the question to understand/interpret?” using a 4-point Likert scale (1=very easy and 4=very difficult). Finally, participants were asked “Is this question upsetting or intrusive” with a simple yes/no response. At the conclusion of the survey, participants had the opportunity to add any additional questions that they felt were important to include.

The Content Validity Ratio (CVR) described by Lawshe [22] was used to assess which items were judged to be most important. The formula utilized was:

$$\frac{\text{Number of raters rating an item 3 or 4} - (\text{number of raters}/2)}{\text{Number of raters}/2}$$

CVR values range from -1.0 to 1.0 with lower numbers indicating less importance and higher numbers indicating greater importance. The cutoff for initial item inclusion was 0.44 based on recommendations by Ayre and Scally [23] based upon the number of raters completing the survey. Given that the patients’ perspective should be weighted more heavily in this process to avoid potential content under-representation [24], items not reaching the cutoff of 0.44 were examined to see how many patients rated the items at a 3-4. Items with >50% of patients rating 3-4 were also included in the initial instrument draft.

Phase 3: Cognitive interviews

Following the initial item reduction process, three-step cognitive interviews were conducted to further validate the items, survey format, and instructions. Participants previously diagnosed with HNC and HNL who did not participate in the initial qualitative interviews or Phase 2 surveys were invited to participate. Potential participants were referred by HNC practitioners and were invited to participate in person, by flyer, or through email correspondence. Cancer and demographic variables were ascertained from the medical record. The Social Deprivation Index [25] was used to characterize socioeconomic status. This index is a composite measure of seven demographic characteristics reported at a zip code level where lower values represent lower community-level disadvantage.

Three-step cognitive interviews were conducted in person or via Zoom video platform by the first author. Three-step cognitive interviews combine the “think aloud” method with probing methods to determine if the participants understand the questions as the researcher intended [26]. During these interviews, participants were first asked to complete the survey, verbally stating what their interpretation of each question was and why they were answering in a particular way. Probing was then conducted to provide additional clarification about item interpretation, response options, and to compare different items. There was intentional exploration of items that were identified as potentially upsetting/intrusive on the Qualtrics survey. Participants were also asked about the instructions and definitions provided. Detailed notes were taken during the interviews and each interview was recorded. The scale was further adapted based on these interviews.

3. Results:

Phase 1:

Based upon thematic analysis of qualitative interviews, 130 unique candidate questions were developed. The binning process identified two major categories: emotional/social and physical/functional. Additionally, there was one global QoL item. Within the category of emotional/social impacts, 5 major bins were identified: appearance, cancer survivor, relationships, worry/vulnerability, and trying to cope. Within the category of physical/functional impacts, 3 bins were established: changes in life participation, discomfort, and functional impairments. Table 1 provides the initial item count for each bin as well as example questions. The winnowing process led to exclusion of 57 items due to redundancy and inclusion of 73 candidate items for further testing.

Table 1: Initial candidate items for QoL survey by bin

	Number of items	Example
Emotional/social		
Appearance items	16	"It bothered me how visible my lymphoedema is"
Cancer survivor	8	"Because of lymphoedema, I was concerned that my cancer would come back"
Relationships	8	"Because of my lymphoedema, I felt less comfortable in social situations"
Worry/vulnerability	16	"I was concerned that lymphedema would cause other health issues in the future"
Trying to cope	31	"I felt like I needed to hide my lymphoedema from others"
Physical/functional		
Changes in life participation	16	"Because of lymphoedema, I tended to avoid social activities"
Discomfort	14	"Because of lymphoedema, moving my head and neck was painful"
Functional impairments	21	"Because of lymphoedema it was difficult to drive"

Phase 2:

A convenience sample of 18 participants completed the Qualtrics survey regarding the candidate questions, 9 clinicians and 9 patients. Most participants were between 31-50 years of age, female, white, and residing in the United States. Demographic information regarding participants is available in Table 2.

Table 2: Participant characteristics at each phase of development

	Phase 1	Phase 2	Phase 3
Medical provider	0	9 (50%)	0
Patient	22 (100%)	9 (50%)	5 (100%)
Age			
18-30 years	0	0	1 (20%)
31-50 years	4 (18%)	11 (61%)	1 (20%)
51-70 years	15 (68%)	6 (33%)	2 (40%)
>70 years	3 (14%)	1 (6%)	1 (20%)
Sex			
Male	11 (50%)	6 (33%)	1(20%)
Female	11 (50%)	12 (66%)	4 (80%)
Ethnicity/race			
White	17 (77%)	13 (72%)	3 (60%)
Black	1 (5%)	1 (6%)	0
Asian	2 (9%)	3 (17%)	2 (40%)
Hispanic	2 (9%)	1 (6%)	0
Country			
USA	15 (68%)	15 (83%)	5 (100%)
UK	7 (32%)	2 (11%)	0
Australia	0	1 (6%)	0

Of the 73 candidate items, 41 met the pre-set criteria using the CVR (Table 3). Of the 32 items that did not meet criteria, 11 were selected by >50% of patients as being “somewhat important” or “very important” and were thus retained. This yielded a total of 52 items to be considered for inclusion on the final scale and 21 items to be discarded. All of the initial 73 candidate items had >50% of participants rating them as “very easy” to understand. Thirteen of the candidate items (25%) had >1 participant indicating it was either “somewhat difficult” or “very difficult” to understand. Of the 52 candidate items, 12 (23%) had more than one participant indicate it was “intrusive/upsetting”. Of the 52 items, 18 reflected physical domains, 10 reflected functional domains, 23 reflected emotional domains, and one was a global item. Response options for the QoL survey were considered, and a 5-point Likert scale was selected.

Table 3: Qualtrics ratings of candidate items

Item	**CVR value**	**# of patients rating as 3 or 4**
Lymphedema has an impact on my quality of life.	0.89	8/9
I feel like people are staring at me because of my lymphedema.	0.18	4/9
Moving my head and neck is painful because of the swelling.	0.53	6/9
My swallowing is difficult because of the lymphedema.	0.65	7/9
My voice doesn't sound normal because of the lymphedema.	0.65	6/9
My speech is unclear when I am swollen.	0.65	6/9
People have difficulty understanding me when I am swollen.	0.65	7/9
I cannot hug friends and family in the same way because of the lymphedema.	-0.18	3/9
It bothers me how visible my lymphedema is.	0.53	6/9
It is difficult to drive because of my lymphedema.	0.29	3/9
My lymphedema impacts my sleep.	0.65	7/9
I don't feel well-rested because of the lymphedema.	0.41	6/9
I avoid sexual activities due to the lymphedema.	0.41	5/9
I cannot kiss as well because of the lymphedema.	0.41	4/9
When I wake up in the morning it is hard to move because of the lymphedema.	0.29	5/9
It is hard to breathe when I am swollen.	0.53	5/9
I lack self-confidence because of my lymphedema.	0.41	4/9
It is difficult to see clearly when I am swollen.	0.53	5/9
I clear my throat a lot because of the swelling.	0.29	6/9
It is difficult to open my mouth when I am swollen.	0.53	6/9
My hearing is worse when I am swollen.	0.53	5/9
It is physically difficult for me to manage my lymphedema.	0.41	4/9
I no longer like the way I look because of the lymphedema.	0.76	6/9
I find it difficult to chew certain foods because of the lymphedema.	0.65	7/9
I worry about the financial impact of my lymphedema.	0.18	4/9
I am not concerned with my lymphedema.	0.41	4/9
Sometimes I stop talking because my speech changes with the swelling.	0.53	5/9

I go to bed early because I am tired of dealing with my lymphedema.	-0.18	2/9
I avoid routine chores outside the house when I am swollen.	0.18	3/9
I look older because of my lymphedema.	0.29	6/9
My lymphedema forces me to disclose to others that I had cancer.	0.41	5/9
My life is not normal because of the lymphedema.	0.76	7/9
My lymphedema makes me worry that my cancer will come back.	0.65	7/9
When I am more swollen, I worry that something else is wrong with my body.	0.53	6/9
I feel isolated from my loved ones because of my lymphedema.	0.29	4/9
I avoid seeing friends and family because of the change in my appearance.	0.53	4/9
I feel like a burden to others due to my lymphedema.	0.18	3/9
I feel like I need to hide my lymphedema from others.	0.78	7/9
I don't like having to talk about my lymphedema to others.	0.29	4/9
I wish that people around me understood my lymphedema better.	0.29	4/9
I am not comfortable with dating or intimacy because of my lymphedema.	0.41	3/9
I feel uncomfortable when people mention my lymphedema.	0.29	2/9
I worry about the impact my lymphedema has on my job or daily activities.	0.53	4/9
There are social activities that I don't participate in due to my lymphedema.	0.53	4/9
My ability to work or do my daily activities has been impacted by my lymphedema.	0.65	5/9
I can't do some activities as long as I would like because of my lymphedema.	0.29	3/9
Because of my lymphedema I choose not to engage in social activities.	0.53	5/9
I cannot enjoy meals with others because of my lymphedema.	0.53	5/9
I avoid looking at myself because of my lymphedema.	0.53	4/9
I never know how my lymphedema will be from day to day.	0.41	5/9
I worry about the lymphedema getting worse in the future.	0.76	7/9
My lymphedema makes me anxious.	0.76	6/9
I am worried that lymphedema may cause other health issues in the future.	0.65	7/9
I worry that if I don't manage the lymphedema now, it will be there forever.	0.76	9/9
I get angry when I am swollen.	0.06	3/9
I hate my lymphedema.	0.41	6/9
I am frustrated by my lymphedema	0.65	7/9
I feel sad when I think about my lymphedema.	0.41	5/9
I am unhappy because of my lymphedema.	0.29	5/9
I am constantly thinking about my lymphedema.	0.29	3/9
I worry about how the lymphedema impacts things like eating, talking, and breathing.	0.65	6/9
Being bothered by my lymphedema makes me feel vain.	-0.18	2/9
I feel like I have no control over my lymphedema.	0.76	7/9
I have accepted that this is the new me.	0.65	7/9
I am hopeful that my lymphedema will improve over time.	0.65	7/9
I am always aware of the lymphedema.	0.53	5/9
I am uncomfortable throughout the day due to the lymphedema.	0.18	3/9
I'm embarrassed by my lymphedema.	0.65	5/9

My lymphedema makes me feel like I'm being strangled.	0.53	5/9
Tightness in my skin makes the lymphedema uncomfortable.	0.29	5/9
My swallowing feels restricted when I am swollen.	0.78	8/9
The swelling feels very stiff and solid.	0.65	8/9
I am unable to turn my head comfortably because of the lymphedema.	0.65	7/9

Phase 3:

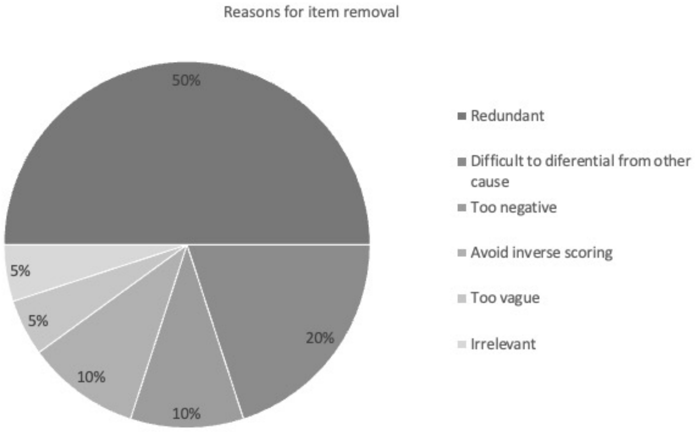
Three step cognitive interviews were performed with 5 individuals. Four of the interviews were conducted on Zoom and one was in person. Participants ranged in age from 29-84 years. Most were female (80%) and white (60%). SDI scores ranged from 4-71 indicating a broad range of population-level disadvantage. HNC diagnoses included tongue (2), oropharynx (1), parotid (1), and carotid sarcoma (1). All participants underwent surgical resection, two had additional radiotherapy, and two had additional chemoradiotherapy. All participants had a history of treatment for HNL within the prior 12-months.

Feedback on instructions: All participants indicated the provided definitions of “lymphoedema” and “quality of life” were helpful in determining how to approach the survey. They similarly reported that the instructions were helpful and necessary. All agreed that the timeline for reflection (past 7 days) would allow for some variation from day to day but not require excessive recall. They all indicated that it was important to include a statement acknowledging the possible presence of other issues, but the need to focus only on the impact of lymphoedema for the purpose of this survey.

Feedback on response options and formatting: The initial format of response options included a 5-point Likert scale ranging from “Strongly Agree” to “Strongly Disagree”. Several participants indicated a preference for a scale that referred more to the frequency of occurrence. Based on this feedback, response options were altered to range from “never” to “always”. All participants preferred a 5-point scale versus a scale with fewer or more options, and landscape rather than portrait layout. Participants indicated that while the survey was slightly long, it was not overly burdensome, and they would be willing to complete this survey in conjunction with clinical visits.

Feedback on items: Based on participant feedback, 20 items were removed. Reasons for item removal included redundancy, difficulty differentiating from other possible causes (e.g. xerostomia), wording judged as too negative, preference to avoid items that would require inverse scoring, vagueness, and irrelevance (Figure 1). Of the remaining items, slight adjustments in wording were conducted to increase clarity. Two additional items were added based on participant feedback. Participants were not concerned about items identified as potentially intrusive/upsetting on the Qualtrics survey. Items indicating “worry” about a concept were changed to “concern” based on feedback. A total of 33 items were retained for the final version of the CALI-HaN. Of the items retained, one item was a global item, 10 reflected physical issues, 7 reflected functional issues, and 15 reflected emotional issues.

Figure 1: Reasons why items were removed following cognitive interviews



4. Discussion:

Applying recommendations for PROM development previously published by the PROMIS and COSMIN groups, particularly in respect to content validity, we have initiated development of an HNL-specific QoL instrument, the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN). Methods employed included a systematic review of the literature and extant scales, qualitative interviews of patients with HNL to identify important concepts and concerns, qualitative analysis to guide item bank development, refinement of the item bank based on patient and practitioner input, and additional, qualitative cognitive interviews to further validate and refine the scale. This instrument is the first of its kind to holistically assess the impact of HNL on physical, functional, and socioemotional outcomes. Inclusion of patient and expert opinions at multiple stages of development contribute to strong content validity.

HRQoL is increasingly accepted as a primary or secondary endpoint in many treatment trials [27-29]. PROMs provide clinicians and researchers the opportunity to understand the patient perspective of the impact of a disease and treatments employed to treat it. Although several tools have been designed for limb lymphoedema, there has been limited focus on measuring QoL in patients with HNL, despite the unique functional consequences experienced in the head and neck region, such as difficulties with voice and swallowing [21]. The HN-LEF Symptom Inventory [19] provides important information about the presence and severity of symptoms in patients with HNL, however, focuses predominantly on physical and functional symptoms rather than emotional consequences. Thus, the CALI-HaN may fill an important gap in the available methods to assess and measure the impact of HNL on QoL.

As with most studies, there are limitations to acknowledge. While purposive sampling was utilized in recruiting patient and expert input at all points of development, those participating in phases 2 and 3 were largely white, female, and from the United States. While the sample in phase 1 was more reflective of the typical HNC demographics in the US and UK, there was overrepresentation of females in phases 2-3 which may limit the degree to which these results can be generalized. It is possible there are missing perspectives based on our use of convenience sampling for the cognitive interviews. Convenience sampling itself may indeed lead to selection bias where participants opting to participate had higher degrees of concern about their lymphoedema. In order to maximize the generalizability of the final instrument, additional validation studies will be conducted using a large, diverse population.

Future work is needed to further assess the validity, reliability, and utility of the CALI-HaN in a large validation cohort of individuals with HNL. Further, psychometric work will be necessary to ensure proper ceiling and floor effects and to establish clinically meaningful change values for this instrument. We are optimistic based on patient and expert feedback that the CALI-HaN will provide valuable insight into the holistic impact of HNL on individual patients.

5. Conclusions:

This study aimed to initiate the development process of a PROM specific to individuals with HNL to assess the impact of HNL on QoL. Data from qualitative interviews demonstrated that physical, functional, and socioemotional effects all need to be considered when measuring QoL in this population. Using methodology recommended by PROMIS and COSMIN, we initiated development of the CALI-HaN, an instrument that shows promise for both clinical and research applications. Future studies of the CALI-HaN's measurement properties will be needed in a large, diverse cross-sectional sample.

Statement of data availability: The data that support the findings of this study are not openly available for patient privacy reasons but may be made available by the corresponding author upon reasonable request.

References:

1. Deng, J., Ridner, S.H., Dietrich, M.S., Wells, N., Wallston, K.A., Sinard, R.J., Cmelak, A.J., & Murphy, B.A. (2012). Prevalence of secondary lymphedema in

patients with head and neck cancer. *Journal of Pain and Symptom Management*. 43(2):244-252. doi:10.1016/j.jpainsymman.2011.03.019

2. Ridner, S.H., Dietrich, M.S., Niermann, K., Cmelak, A.J., Mannion, K., & Murphy, B.A. (2016). Prospective study of the lymphedema and fibrosis continuum in patients with head and neck cancer. *Lymphatic Research and Biology*. 14(4):198-205. doi:10.1089/lrb.2016.0001
3. Deng, J., Murphy, B.A., Dietrich, M.S., Wells, N., Wallston, K.A., Sinard, R.J., Cmelak, A.J., Gilbert, J., & Ridner, S.H. (2013). Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. *Head and Neck*. 35(7):1026-1035. doi:10.1002/hed.23084
4. Murphy, B.A. & Ridner, S. (2010). Late-effect laryngeal oedema/lymphoedema. *Journal of Lymphoedema*. 5(2): 92-3.
5. Nixon, J.L., Pigott, A.E., Cartmill, B., Turner, J., Fleming, J., & Porceddu, S.V. (2018). A mixed methods examination of distress and person-centred experience of head and neck lymphoedema. *Oral Oncology*. 83:18-24. doi:10.1016/j.oraloncology.2018.05.025
6. Deng, J. & Murphy, B.A. (2016). Lymphedema self-care in patients with head and neck cancer: a qualitative study. *Supportive Care in Cancer*. 24(12):4961-4970. doi:10.1007/s00520-016-3356-2
7. Constitution of the World Health Organization. In: *World Health Organization: Basic Documents. 45th Ed*. Geneva: World Health Organization; 2005.
8. Beelen, L.M., van Dishoeck, A.M., Tsangaris, E., Coriddi, M., Dayan, J.H., Pusic, A.L., Klassen, A., & Vasilic D. (2021). Patient-reported outcome measures in lymphedema: a systematic review and COSMIN Analysis. *Annals of Surgical Oncology*. 28(3):1656-1668. doi:10.1245/s10434-020-09346-0
9. Roick, J., Danker, H., Dietz, A., Papsdorf, K., & Singer, S. (2020). Predictors of changes in quality of life in head and neck cancer patients: a prospective study over a 6-month period. *European Archives in Otorhinolaryngology*. 277(2):559-567. doi:10.1007/s00405-019-05695-z
10. Mehanna, H.M. & Morton, R.P. (2006). Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clinical Otolaryngology*. (3):204-211. doi:10.1111/j.1749-4486.2006.01188.x
11. Sunderland, M., Matthews, C., Waterhouse, D., Shetty, S. & Morton, R.P. (2023). Unmet needs, quality of life and psychological distress: insights regarding head and neck cancer patients in a rural setting. *The Journal of Laryngology and Otology*. 137(1):89-95. doi:10.1017/S0022215121001699
12. Patterson, J.M., Lu, L., Watson, L.J., Harding, S., Ness, A.R., Thomas, S., Waylen, A., Pring, M., Waterboer, T., & Sharp, L. (2022). Associations between markers of social functioning and depression and quality of life in survivors of head and neck cancer: Findings from the Head and Neck Cancer 5000 study. *Psychooncology*. 31(3):478-485. doi:10.1002/pon.5830
13. Lin, B. M., Starmer, H. M., & Gourin, C. G. (2012). The relationship between depressive symptoms, quality of life, and swallowing function in head and neck

cancer patients 1 year after definitive therapy. *The Laryngoscope.122*(7): 1518–1525. doi:10.1002/lary.23312

14. Higginson, I.J. & Carr, A.J. (2001). Measuring quality of life: Using quality of life measures in the clinical setting. *BMJ (Clinical Research ed)*. 322(7297):1297-1300. doi:10.1136/bmj.322.7297.1297
15. DeWalt, D.A., Rothrock, N., Yount, S. & Stone, A.A.; PROMIS Cooperative Group. (2007). Evaluation of item candidates: the PROMIS qualitative item review. *Medical Care*. 45(5 Suppl 1): S12-S21. doi:10.1097/01.mlr.0000254567.79743.e2
16. Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., Bouter, L. M., & de Vet, H. C. (2010). The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*. *19*(4): 539–549. doi:10.1007/s11136-010-9606-8
17. Deng, J., Ridner, S.H., Murphy, B.A., & Dietrich, M.S. (2012). Preliminary development of a lymphoedema symptom assessment scale for patients with head and neck cancer. *Supportive Care in Cancer*. 20(8): 1911-8.
18. Deng, J., Murphy, B.A., Niermann, K.J., Sinard, R.J., Cmelak, A.J., Rohde, S.L., Ridner, S.H., & Dietrich, M.S. (2022). Validity testing of the Head and Neck Lymphedema and Fibrosis Symptom Inventory. *Lymphatic Research and Biology*. 20(6):629-639. doi:10.1089/lrb.2021.0041
19. Ridner, S. H., Deng, J., Doersam, J. K., & Dietrich, M. S. (2020). Lymphedema Symptom Intensity and Distress Surveys— Truncal and Head and Neck, Version 2.0. *Lymphatic Research and Biology.* 19(3): 240-8. https://doi.org/10.1089/lrb.2020.0071
20. Starmer, H.M., Cherry, M.G., Patterson, J., Young, B., & Fleming, J. (2023). Assessment of measures of head and neck lymphedema following head and neck cancer treatment: a systematic review. *Lymphatic Research and Biology*. 21(1):42-51. doi:10.1089/lrb.2021.0100
21. Starmer, H. M., Cherry, M. G., Patterson, J., Fleming, J., & Young, B. (2023). Head and neck lymphedema and quality of life: the patient perspective. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*. *31*(12): 696. https://doi.org/10.1007/s00520-023-08150-2
22. Lawshe, C. (1975). A quantitative approach to content validity. *Personnel Psychology*. 28(4): 563-75. Doi: 10.1111/j/1744-6570.1975.tb01393.x
23. Ayre, C. & Scally, A.J. (2014). Critical values for Lawshe's Content Validity Ratio. *Measurement and Evaluation in Counseling and Development.* 47:1, 79-86, doi: 10.1177/0748175613513808
24. Almanasreh E., Moles R., & Chen T.F. (2019). Evaluation of methods used for estimating content validity. *Research in Social and Administrative Pharmacy.* 15(2): 214-21.
25. Robert Graham Center. Social Deprivation Index (SDI). 2018.

26. DeVet, H.C.W., Terwee, C.B., Mokkink, L.B., & Knol, D.L. (2018). *Measurement in Medicine*. Cambridge University Press, Cambridge UK.
27. Weiss, M.L., Domschikowski, J., Krug, D., Sonnhoff, M., Nitsche, M., Hoffmann, W., Becker-Schiebe, M., Bock, F., Hoffmann, M., Schmalz, C., Dunst, J., & Fabian, A. (2023). The impact of palliative radiotherapy on health-related quality of life in patients with head and neck cancer - Results of a multicenter prospective cohort study. *Clinical and Translational Radiation Oncology*. 41:100633. Published 2023 Apr 26. doi:10.1016/j.ctro.2023.100633
28. McDowell, L., Bressel, M., King, M.T., Corry, J., Kenny, L., Porceddu, S., Wratten, C., Macann, A., Jackson, J.E., & Rischin, D. (2023). Patient-reported symptom severity, health-related quality of life, and emotional distress trajectories during and after radiation therapy for human papillomavirus-associated oropharyngeal cancer: a TROG 12.01 secondary analysis. *International Journal of Radiation Oncology, Biology, Physics*. 116(5):1110-1125. doi:10.1016/j.ijrobp.2023.02.041
29. Rischin, D., Harrington, K.J., Greil, R., Soulieres, D., Tahara, M., de Castro, G., Jr, Psyrri, A., Brana, I., Neupane, P., Bratland, A., Fuereder, T., Hughes, B.G.M., Mesia, R., Ngamphaiboon, N., Rordorf, T., Ishak, W.Z.W., Hong, R.L., Mendoza, R.G., Jia, L., Chirovsky, D., … Burtness, B. (2022). Pembrolizumab alone or with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: Health-related quality-of-life results from KEYNOTE-048. *Oral Oncology*. 128:105815. doi:10.1016/j.oraloncology.2022.105815

8. Overall discussion, conclusions, and next steps

8.1. Chapter overview

The purpose of this final chapter is to synthesise the accomplishments of this thesis and to frame this work in the context of the existing literature. I will revisit the primary aims developed at the onset of this thesis and discuss how each of these aims were met. Additionally, I will discuss strengths and limitations of this thesis. I will highlight ways in which this research may influence clinical and research practices and will outline planned future directions for additional validation of the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN).

8.2. Primary aims of this thesis

At the onset of this thesis, there was a void in the HNL literature regarding measures that may capture the comprehensive patient experience of living with HNL. The Lymphedema Symptom Intensity and Distress Survey - Head and Neck (LSIDS-HN) was first described in 2012 as a tool to measure the presence and severity of symptoms associated with HNL (Deng et al., 2012; Deng et al., 2016). It was revised in 2020 (Ridner et al., 2020) to reduce the length and complexity of the instrument. In 2021 the instrument was further adapted and re-named the Head and Neck Lymphedema and External Fibrosis Symptom Inventory (HN-LEF Symptom Inventory) (Deng et al., 2021). Each iteration of this instrument focused primarily on the physical repercussions of HNL, with much less emphasis on the socioemotional and functional impacts of HNL. Additionally, these scales were validated on oral and oropharyngeal cancer patients only, therefore are not necessarily generalisable for use with other HNC populations such as individuals with laryngeal, hypopharyngeal, and thyroid cancer. Due to the lack of availability of an instrument that looks at HNL specific HRQoL more globally, this thesis was designed to initiate the process of filling that void.

The primary aim of this thesis was to explore *patient perspectives* of living with HNL with a goal of developing an HNL-specific HRQoL PROM that may be used for clinical and research purposes. Additionally, I sought to gather insights of the multidisciplinary HNC team regarding their perceptions of HNL and its impact on patients. This research had four primary objectives as described in Chapter 1.

- Objective 1: To identify the measures currently used in the assessment and measurement of HNL and to assess their validity and reliability. I sought to gain a better understanding of the adequacy and comprehensiveness of available measures to establish if it would be appropriate and beneficial to initiate development of a new instrument. This was accomplished through a systematic review guided by the COSMIN framework (Study 1, Chapter 3). This review revealed that there is not a validated tool available that assesses all aspects of HNL-related QoL.
- Objective 2: To identify how HNL may impact HRQoL. Based on the results of my systematic review revealing the absence of an HNL-specific HRQoL PROM, a decision was made to move forward with the

development of such a PROM. As a result, and consistent with good practice guidelines, I sought to gain a richer understanding of the myriad of ways in which HNL may impact HRQoL. This was accomplished through completion of a series of semi-structured qualitative interviews with individuals with HNL (Study 2, Chapter 6). These interviews revealed a broad range of impacts of HNL on HRQoL in a diverse sample of participants with HNL.

- Objective 3: To develop potential items to form the basis of a HRQoL instrument based on qualitative interviews of individuals with HNL. This initially involved generating a candidate item bank based upon the qualitative interviews described in Chapter 6. Subsequently, these candidate items were assessed through completion of online surveys and interviews with key stakeholders including patients with HNL and clinical providers with expertise in HNC and HNL (Study 3, Chapter 7). The item bank was adapted based on this feedback and through binning and winnowing and yielded a prototype version of the CALI-HaN.
- Objective 4: To refine the CALI-HaN for further field testing and validation. Once an item bank was developed and refined, there was a need for additional stakeholder/patient feedback on the content and format of the pilot instrument. This was accomplished via three-step cognitive interviews of patients with HNL (Study 3, Chapter 7). The CALI-HaN was further adapted based upon these interviews.

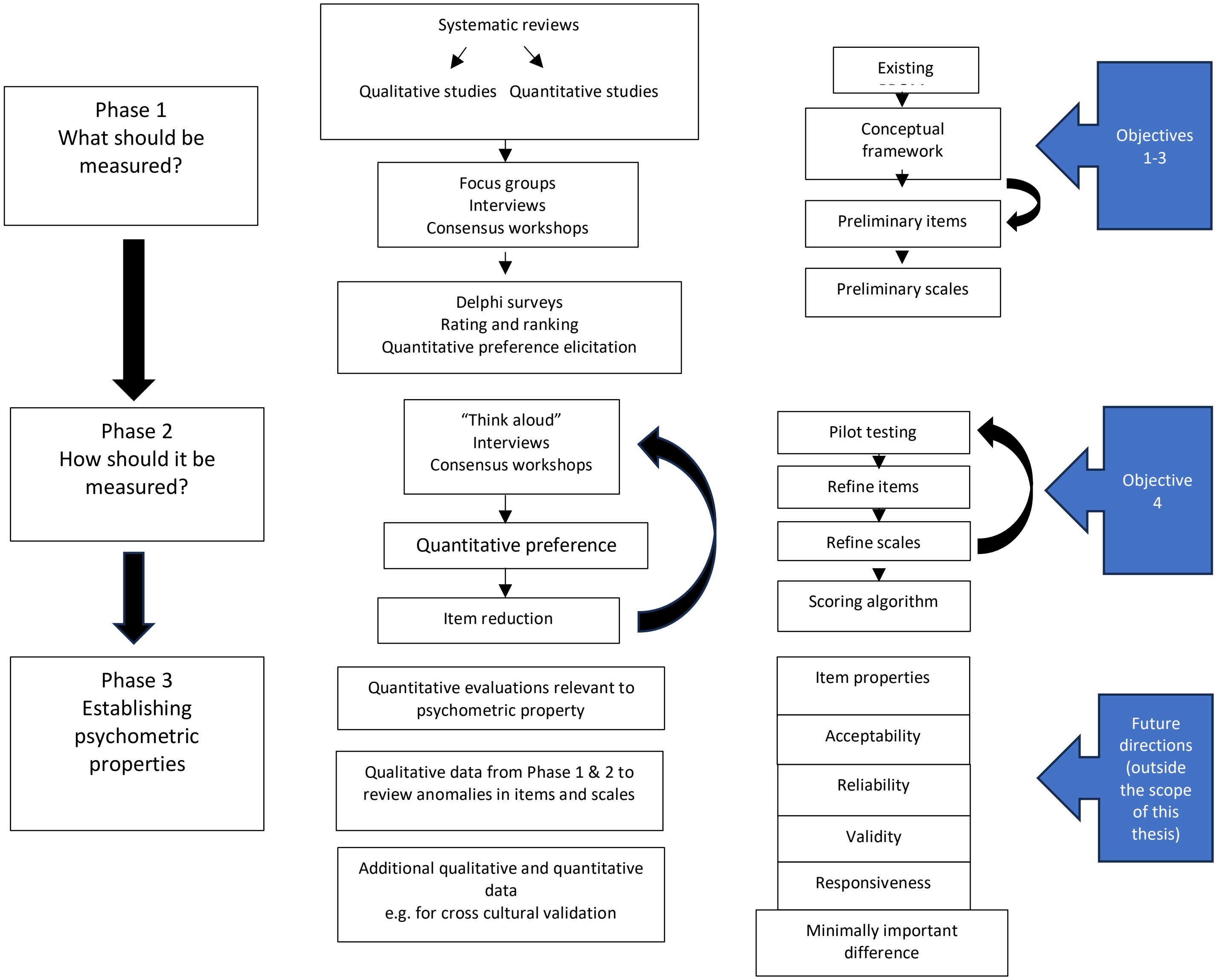
8.3. Summary of main findings

Patients with HNC are at risk of developing HNL which may have a substantial impact on function and HRQoL. The systematic review presented in Chapter 3 identified that several measures have been used to quantify or describe HNL, however many of those measures lack validation and reliability data. The instruments judged to be of highest quality included the HN-LEF Symptom Inventory (Deng et al., 2012; Deng et al., 2016; Deng et al., 2021) and the Revised Patterson Oedema Scale (Patterson et al., 2007; Starmer et al., 2021). Unfortunately, neither of those scales adequately measure the impact of HNL on an individual patient, particularly regarding socioemotional outcomes. Thus, I proceeded to develop an HNL-specific HRQoL instrument, guided by COSMIN recommended methods and with a particular emphasis on patient participation in all stages of development.

Qualitative interviews with individuals with HNL identified multiple physical, functional, and emotional impacts of HNL. Major categories of HNL impact included issues around appearance and identity, perceptions of change in identity to being a cancer survivor, changes in relationships, an increased sense of vulnerability, attempts to cope with changes, changes in participation in meaningful life activities, physical discomfort, and functional impairments. It was important that each of these were encompassed by the PROM under development.

For this thesis, PROM development included item generation and survey refinement with substantial patient and clinician feedback. Item generation was based on qualitative interviews with patients in the UK and US living with HNL. Item refinement and scale adaptation were based on patient and clinician feedback. Three-step cognitive interviews were used to further validate the content and format of the prototype instrument. Inclusion of patient and clinician perspectives at all points of PROM development have contributed to strong content validity. The resultant prototype, which I termed the Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN) is now ready for further validation and field testing. As I will discuss in section 8.8 below, this will include establishing concurrent and structural validity, reliability, and responsiveness. Figure 8-1 reviews the framework for PROM development which guided this thesis where Phase 3 demonstrates the future directions that need to be completed prior to utilisation of the CALI-HaN for clinical care or outcomes research.

Figure 8-1 Thesis mapped to Howell's development process for patient-reported outcome measures (Howell et al., 2022)



8.4. Implications for clinical practice and research

When the CALI-HaN is finalised, it is anticipated that it will impact both clinical practice and research. As discussed in Chapter 5, PROMs are increasingly being used not just in outcomes research, but also in clinical practice, particularly in oncology clinics. Thus, it is important to reflect on how the CALI-HaN may be used in both settings.

8.4.1. Clinical practice implications

Rehabilitation professionals are increasingly required to demonstrate the impact of treatments provided. Documentation of meaningful clinical outcomes provides payors with evidence of return on investment or “quality of care”. At the same time, patients have become more informed and more interested in knowing how they are (or are not) progressing in therapy. Thus, clinicians need to have metrics that will allow them to demonstrate change in response to treatment. As discussed in Chapter 4, discordance is often seen between measures of physiology, functional impact, and HRQoL (Ashley et al., 2015; Hulbert-Williams et al., 2012; Wakefield, 2009). Thus, measures that only assess physical function may fail to demonstrate benefits in patient perceived function and HRQoL. The CALI-HaN was developed with this need in mind and aimed to provide a method for clinicians to capture patient-perceived changes in HNL specific HRQoL.

In addition, the availability of an instrument such as the CALI-HaN that captures the patient perspective will assist clinicians in understanding the impact of HNL-related HRQoL on an individual patient. This may facilitate clinician’s identification of previously unknown concerns and/or trigger appropriate interventions. For example, if a patient reports a high level of emotional impact related to their HNL via the CALI-HaN, they may be referred for psychosocial counseling with a qualified clinical psychologist to learn how to process, adapt to, or overcome their difficulties (Arif et al., 2023; Semple et al., 2004; Semple et al., 2009). In contrast, a patient who primarily reports issues with pain and discomfort on the CALI-HaN may receive further follow up in the HNC care center, be referred for physiotherapy, or be referred to a pain management clinic (Blasco et al., 2020; Cho et al., 2019; Mirabile et al., 2016). Using a comprehensive PROM may allow for more efficient identification of patient concerns in comparison to the extensive clinical conversations that might be required to elicit similar information (Campbell et al., 2002; Rogers et al., 2009). It has been demonstrated that clinicians using PROMs are more likely to address patient needs than those using standard clinical practices without PROMs (Detmar et al., 2002).

There has been some inconsistency in the literature regarding patient perceptions of PROMs. A systematic review by Campbell et al. (2022) evaluated 50 studies looking at patient and/or clinician perspectives of using PROMs. They identified commonly reported benefits such as promotion of patient involvement in care, increased focus on areas of importance during clinic visits, enhanced patient-centered care, consistent monitoring of status across time, and improved patient-provider relationships. Despite these benefits, they also found some limitations to using PROMs including unrealistic patient expectations for care, a lack of elicitation of pertinent clinical information, and suitability across a patient population. Of note, Recinos et al. (2017) found the greatest patient reported benefits in those who reported their care providers reviewed the results of the PROM with the patient during their consultation. When a provider reviewed the results of the PROM with patients, there was a 6.6-fold increase in patients perceiving PROMS as beneficial. Thus, the value of a PROM does not lie solely in the instrument, but also in the way in which it is utilised.

There are known barriers in the integration of PROMs into clinical practice such as clinician buy-in, increased visit times, increased need for clinical support staff, and patient access challenges due to issues such as visual impairment, cognitive limitations, and language differences (Agarwal et al., 2022; Eton et al., 2014). Because of such challenges, it is important to consider parameters around implementation and utilisation of the CALI-HaN. As such, I conducted stakeholder engagement interviews with five HNL clinicians in a variety of settings to ascertain their perspectives regarding implementation of the CALI-HaN. Although not the primary focus of this thesis, these interviews were extremely valuable and provided various perspectives that informed my decision-making during development of the CALI-HaN. These interviews were primarily conducted with rehabilitation professionals (physiotherapists and SLTs), though I also had informal discussions with physicians engaged in HNL care.

Each clinician I interviewed indicated they felt the CALI-HaN was an important and valuable addition to the HNL assessment toolbox. Considerations raised during these conversations included the need for a succinct instrument that would not be burdensome to implement in the clinical setting, a global item to estimate the impact on HRQoL broadly, and responsiveness to detect change over the course of treatment. These experts agreed that an HRQoL tool specific to HNL would be used primarily to track changes over time, but also indicated that specific domains of concern might be instructive for the identification of patient-centered goals of treatment. Additionally, the CALI-HaN would help a rehabilitative therapist work with a patient to determine when to continue, adapt, or discontinue therapy based upon their changes in HNL-related HRQoL. Further, it is possible that in the future, the CALI-HaN might be used by members of the cancer care team to determine when referrals for lymphoedema therapy may be indicated. However, further work would be required to establish such criteria or guidelines.

8.4.2. Research implications

From a research perspective, my systematic review identified a lack of a standard approach to measuring HNL in clinical research. Because HNL is multidimensional, it must be assessed using a combination of outcome measures in clinical effectiveness research. This may include tape measures such as those described in the ALOHA protocol (Purcell et al., 2014) or the MD Anderson method (Smith & Lewin, 2010), grading of internal oedema using the Revised Patterson Oedema Scale (Patterson et al., 2007; Starmer et al., 2021), symptom inventories such as the HN-LEF Symptom Inventory (Deng et al., 2021), and severity grading such as the Foldi or MD Anderson scales (Smith & Lewin, 2010). Following additional validation work, future investigators may also include a measure of patient-perceived HRQoL using the CALI-HaN. Development of a core outcome set (COS) for HNL may be a valuable future endeavor (Hughes et al., 2022; Williamson et al., 2017).

8.5. Strengths and limitations

Strengths and limitations of each study have been discussed in their respective manuscripts. In this section, I will discuss overall strengths and limitations that apply broadly to this thesis.

A major strength of this thesis is the consideration of the perspectives of a diverse sample of patients living with HNL. Understanding the lived experience of those with any health condition is highly valuable in both clinical and research settings. This is particularly salient in research endeavors where the construct of interest is one that can only be observed by the patient. The insights of these participants about what it is like to struggle with HNL substantially enriched my understanding and complimented my observations based on prior clinical experiences. The participants' willingness and desire to share their difficulties highlighted the need to create an instrument that would allow clinicians to have greater insights into their patients' challenges, to provide truly patient-centered care and to develop patient-centered interventions. In contrast to prior qualitative work, the sample of participants for this thesis was more heterogenous, including both men and women, a variety of racial/ethnic backgrounds, young and old participants, and those with a variety of primary tumour locations. The purposive sampling employed allowed me to ascertain a more comprehensive understanding of the impact of HNL on HRQoL.

Another major strength of this thesis is the insight I gained by including clinicians' and researchers' perspectives alongside the voice of the patients. This thesis benefitted from the input of a variety of professionals including rehabilitation specialists, researchers, surgical oncologists, medical oncologists, and radiation oncologists. Their input about the value of an HNL-specific HRQoL tool validated that this endeavor was worthwhile and not merely important to me. Further, their input about implementation considerations was extremely valuable to ensure that the instrument under development would be feasible for use in a clinical setting.

As discussed in Chapters 2 and 3, several HNL measures exist that focus on the *impairment* level of the WHO ICF framework. This includes the one PROM designed for HNL, the HN-LEF Symptom Inventory, which focuses predominantly on symptoms and symptom burden, but is less focused on *activity* and *participation*. One of the strengths of this thesis and the CALI-HaN is the holistic assessment of HRQoL domains including impairment, activity, participation, and patient-perceived well-being. This takes into consideration that personal and environmental factors may influence the degree to which an impairment may impact an individual's HRQoL and provides a more robust picture of HRQoL related to HNL than is possible with extant scales and measures.

Another major strength of this work is the methodological rigor implemented at all phases of this thesis. For my systematic review I utilised the PRISMA checklist (Page et al., 2021) for systematic reviews to ensure all critical and relevant data points were included in this publication. Similarly, the SRQR checklist was utilised in the reporting of my qualitative interviews (O'Brien et al., 2014). In the development of the CALI-HaN, I was guided by the PROMIS (DeWalt et al., 2007) and COSMIN (Mokkink et al., 2010) methodological guidelines for PROM development. Integrating these best practice guidelines at all stages elevated the quality of this thesis and ensured appropriate rigor.

One factor that might be considered either a strength or a limitation of this thesis is the clinical expertise I brought to this work. As a clinician working with patients with HNC for over 20 years and HNL for ~7 years, my prior experience provides both deep insight about these individuals and their experiences, but also potential bias because of those experiences. This was a very important point to consider, particularly during the completion and analysis of qualitative interviews. It was critical that I remained mindful of this potential bias so that I did not ask participants leading questions during interviews. I needed to focus on listening and fully exploring their experience through their words, not through the filter of my own experiences. Similarly, when performing qualitative analysis, I needed to remain focused on the message that that participants were sharing, not my own thoughts and feelings based on prior experiences. It was critical that I considered my dual role as clinician and researcher at all stages of this work.

One limitation to this work relates to the patients sampled during the qualitative interviews and the later three-step cognitive interviews. Despite efforts to purposively sample a diverse group of participants, participants were reflective of the populations served in the HNC centers in Liverpool and at Stanford, which means that there may be some perspectives that were missed. For example, whilst participants from various ethnic/cultural backgrounds were included, in many cases these were singular voices which may not completely represent the voices of those groups. I intentionally included different participants for the different stages of the qualitative work to elicit a broader representation, however even with these efforts taken, the overall sample included a misrepresentative proportion of female patients for a HNC population and was overwhelmingly White. Further, due to the use of video interviews, our sample was limited to those with access to the internet. Cross-cultural validation may be necessary in countries with patient demographics dissimilar to our sample.

Additionally, the lack of objective data about lymphoedema severity in the participants may be considered a limitation. Because of my pragmatic sampling, not all participants had completed formal assessment of their lymphoedema from an HNL specialist. Thus, it is possible that this sample does not represent the full spectrum of lymphoedema severity, which could, in turn influence the degree of influence of the lymphoedema on HRQoL. I attempted to control for this by using standard data saturation considerations during recruitment, however there is some potential that not all perspectives were available. Nevertheless, as previously discussed, the degree of physiologic impairment does not always correlate to the degree of impact on activity and participation, so given that I achieved data saturation during the qualitative studies, I am less concerned about the impact that lymphoedema severity may have had on the outcomes of this research.

Another potential limitation is the degree to which patients were involved at all stages of this thesis. Organisations such as the National Institute for Health Care Research (NIHR) and the Patient-Centered Outcomes Research Institute (PCORI) advocate for full patient and public involvement in research (NIHR, 2024; PCORI, 2023). These guidelines highlight the difference between patient involvement (research is done with patients and involves a great degree of shared decision-making) and patient participation (where individuals are consented to be part of the study). Consistent with COSMIN guidelines, this thesis incorporated a good deal of patient participation, however, it did not engage patients to the same degree regarding planning and performing the research. There could have been value in involving patients and caregivers from the onset of the thesis to integrate their perspectives into the methodology employed and decisions made during the research process.

8.6. COVID impacts and reflections

When I embarked upon my doctoral studies in 2019, I, like the rest of the world, had no expectation that months later we would be plunged into a global pandemic. Although my initial intent was to remain based in the US during my research work, I had intended to travel to Liverpool at least once per year during my doctoral work. Unfortunately, travel restrictions during the pandemic limited this to only one visit to Liverpool whilst I conducted my research. However, the availability of video conferencing allowed me to meet with my committee frequently, thereby reducing the potential disruption of my research.

As previously mentioned, the ability to use video conferencing did open the opportunity to interview participants in the US and UK despite travel limitations during the pandemic. This allowed me to gain a broader understanding of patient perspectives in individuals with HNL. Some of the different experiences reported by participants in these two countries highlighted how the distinctive healthcare systems and cultural norms in each country may influence patient-perceived outcomes. This observation may be interesting to explore in future research.

In addition to the practical implications of using video conferencing for this thesis, the changes in healthcare provision because of the pandemic should be considered in the context of PROM development. Traditionally, clinical care in the UK and US has been largely based on an in-person care model. Hence, PROMs have generally been administered on paper, or more recently, electronically during a clinical encounter. The increase in use of telehealth because of the pandemic suggests the need to consider alternative ways of administering PROMs. ePROMS have received increasing attention, with more publications on ePROMS published in 2023 alone, compared to 1980-2019 combined (PUBMED, 2023). Preliminary studies have demonstrated ePROMs are considered practical and helpful for both patients and clinicians (Lombi et al., 2023; Payne et al., 2023; Tsubaki et al., 2022). This suggests the need to consider multiple administration options for the CALI-HaN during future validation work.

8.7. General reflections

My experience in completing this thesis has been highly enriching. I have learnt a great deal about qualitative research and see this as a tool that I will certainly utilise in future research. Having the opportunity to work with two psychologists with a research philosophy and skill set so different from my own has been invaluable. I feel very fortunate to have had the opportunity to hone these skills under their tutelage. I have also learnt a great deal about PROM development that will serve me well not only in further developing the CALI-HaN, but when evaluating and considering other tools for use in clinical or research applications.

As a clinical researcher with a substantial background in quantitative research approaches, the integration of mixed methods into this thesis allowed me to learn new skills, but more importantly enabled me to look at the work through a different lens. After more than 20 years of clinical practice, I have found myself questioning the positivist ontological assumptions within the field of medicine. It has become increasingly apparent to me that there is not often one ‘truth’ that can be directly observed and measured. This is particularly salient when trying to take a person-centered approach to measuring treatment outcomes. It is not enough to merely measure structural changes or physiologic differences to uncover truth. We must also consider the context in which the individual needs to function to truly understand their challenges and the relative impact of interventions.

This thesis has allowed me to embrace a more constructionist approach – acknowledging that when human beings are involved, reality is not fixed, but somewhat subjective and malleable. This is particularly important in my clinical and research interests concerning patient outcomes which are by nature subjective. For example, whilst it is important to try to establish “truths” surrounding which treatments may be more effective in treating a condition, I have a greater appreciation for acknowledging variability when applying empirically established data to an individual, particularly in the context of complex clinical decision making. I feel that going forward, I will approach my research and clinical care using a more open, patient-centered approach.

In addition to changes in my philosophical approach, what I learnt interviewing patients with HNL was so much deeper than what I had previously gleaned from my clinical experiences with those patients that I had a prior clinical relationship with. This highlighted that whilst we may discuss patient preferences and experiences in the clinical setting, we are likely just scratching the surface on their reality. As a clinician, I think I will be more mindful of the need to elicit this information from patients, whether through use of an instrument like the CALI-HaN, or through clinical conversations.

8.8. Future directions

In this thesis, I have provided an overview of the existing qualitative literature regarding HNL. One possible future direction would be to extend this to a formal, qualitative evidence synthesis (Dixon-Woods, 2005). An integrative approach would help to synthesise or summarise prior studies whereas an interpretive approach could be utilized to develop theoretical understandings of HRQoL in individuals with HNL. Such a synthesis may be of particular value for the development of patient-centered intervention approaches.

Whilst efforts to date were designed to initially develop and prioritise the content validity of the CALI-HaN, additional testing is needed prior to utilisation of the scale in clinical or research applications. Field testing (as will be described in the following sections) is the most logical next step to further assess the validity, reliability, and responsiveness of the CALI-HaN in a larger patient sample and is supported by guidance provided by the EORTC (2011) and COSMIN (2019). Additionally, field testing will allow me to assess for floor or ceiling effects to ensure the CALI-HaN is adequately able to discriminate between patients at the extreme ends of the scale (deVet et al., 2018). I anticipate that a sample size of >100 will likely be necessary to achieve these goals, based on best practice guidance (McKenna, 2011). Additionally, I would like to be intentional about sampling from a diverse patient population. Therefore, field testing will likely involve a multi-institutional study. I have discussed the potential for collaboration with clinician researchers at the University of Pittsburgh and the MD Anderson Cancer Center and there is enthusiasm to collaborate on this work. Additionally, in the future, there could be value in validation in populations other than HNC, such as burn victims.

8.8.1. Examining Item Scores

Following pilot testing and cognitive interviews, it is important to examine item performance in a larger sample that is reflective of the population for which the instrument was developed. Missing scores are one dimension which should be examined to determine whether items are unclear or whether the available response options may not suit particular items. Missing scores may also suggest intrusiveness of items. DeVet et al. (2018) suggest that <3% of scores missing is acceptable whilst >15% of missing scores would be considered unacceptable. Items with a high percentage of missing scores should be removed and/or replaced depending upon the perceived importance of the item.

8.8.2. Item score distribution

Another important consideration for field testing is regarding score distribution. This allows the researcher to determine if all response options are informative and important to retain. Here the distribution of the responding population using each response option can be examined using frequency tables. If particular response items are underutilised, I may consider removing them from the scale.

8.8.3. Item clustering

In a multi-item instrument, it is important to consider how individual items correlate. Factor analysis can be used to determine which items do and do not correlate with each other. Determining these meaningful clusters contributes to interpreting results and is important for validity testing. The inter-item correlations can be examined and those items correlating closely can be grouped into domains. These domains may be used later for comparison with similar domains on the HN-LEF Symptom Inventory and UWQOL to establish concurrent validity (see below).

8.8.4. Validity testing

Content validity, or the degree to which the instrument measures what it purports to measure was integrated into the initial development of the CALI-HaN. This was accomplished through integration of patient perspectives and the input of expert clinicians. Following good practice guidelines established by the COSMIN collaborative, we have confidence that the CALI-HaN has good content validity.

8.8.4.1. Concurrent validity

Because there is not a gold-standard in the assessment of HNL HRQoL, we are unable to establish criterion validity. This is a common issue for many PROMs, particularly those that focus on HRQoL (Frost et al., 2007). Rather, our future validation efforts will focus on establishing concurrent validity. To establish concurrent validity, we will look at how the CALI-HaN performs relative to the HN-LEF Symptom Inventory (Deng et al., 2021) and a general HNC HRQoL instrument, the University of Washington QoL instrument (UWQoL) (Weymuller et al., 2001). Though the HN-LEF Symptom Inventory provides some perspective on the types of symptoms that patients associate with HNL, it does not provide that information about the subjective impact on well-being. Thus, it important to also include a general measure of HRQoL. The UWQoL (Version 4.1) has 14 single domain questions (e.g. pain, appearance, activity) as well as three global questions about overall HRQoL (Rogers et al., 2002; Rogers et al., 2010; Weymuller et al., 2000; Weymuller et al., 2001). A physical score and a social-emotional score can be calculated based on patient responses. There are several other HNC HRQoL scales such as the EORTC-QLQ-HN35 (Singer et al., 2013) and the FACT-HN (Cella et al., 1993). Whilst each of these HRQoL instruments have undergone validation and are appropriate for use within the HNC population (Gourin, 2014; Ojo et al., 2012), I selected the UWQoL for validation because it is free, short, and contains items like those in the CALI-HaN that may be examined during analysis.

8.8.5. Reliability

The reliability of a measure refers to the “degree to which a measure is free from measurement error” (Mokkink, 2010a) as well as the relative stability of scores over time when the underlying construct has not changed. Generally, multi-item PROMs have better reliability than single-item instruments as they are less prone to random error (deVet et al., 2018). Internal and test-retest reliability can be calculated to establish reliability of a PROM. Cronbach’s coefficient α is a measure of reliability in multi-item scales and may be used to assess the internal reliability of an instrument as well as its reliability over time. To measure test-retest reliability, I will have participants complete the CALI-HaN at the time of referral for lymphoedema assessment as well as at the time of the initial lymphoedema evaluation. As the duration of time between referral and assessment is typically 7-14 days in our HNL clinic, we would not anticipate substantial differences in HNL-specific HRQoL during that time.

8.8.6. Responsiveness

Responsiveness is like validity, however, refers to the ability of an instrument to detect change over time. This is particularly important with a scale like the CALI-HaN which we hope will be sensitive to changes over time related to disease state and treatment response. When measuring responsiveness, it is important that the period between measures be long enough that change in the construct would be anticipated (deVet et al., 2018). As such, I will plan to administer the CALI-HaN prior to initiation of HNC treatment, prior to HNL treatment, and then again 3 months following initiation of treatment to measure for instrument responsiveness. By including timepoints prior to development of HNL and after HNL treatment, we will be able to identify bi-directional changes in scores.

Similarly, it is important to consider what is clinically meaningful change on repeated PROMs. Because of the subjectivity of patient reported outcomes, it is important to acknowledge that what is clinically relevant to one person may not be important to another. Thus, many academics use the term “minimal important change” or MIC to refer to the smallest change which a patient might perceive to be important.

Crosby et al. (2003) describe two main techniques for establishing clinically meaningful changes using PROMS, anchor-based approaches and distribution-based methods.

Anchor-based approaches compare the results of the target instrument to another established instrument to determine what is a meaningful difference on the target instrument. For example, if a new instrument was developed to measure HRQoL relative to swallowing, the anchor instrument may be standardised diet levels such as the Functional Oral Intake Scale (FOIS) (Crary et al., 2005). The FOIS is a 7-point scale used to describe different levels of diet complexity. A researcher might select a one-point change in FOIS scores as clinically meaningful. The mean change in scores in those meeting the criteria for meaningful difference on the FOIS would then be considered the minimally important difference score for the new instrument. One of the challenges in using an anchor-based approach is regarding the availability and validity of an anchor.

In contrast, distribution-based methods are based on statistical characteristics of a participant sample. They consider whether the measured change is greater than would be expected due to random variation. The primary limitation to distribution-based methods, particularly for PROMs is that they do not take into consideration the importance of the measured change. Thus, whilst something might be determined to be important using these techniques, it may be a meaningless difference from a patient perspective.

Because of the limitations in both anchor-based and distribution-based methods, Crosby et al. (2003) advocate for using a combination of anchor-based and distribution-based methods. DeVet et al. (2007) proposed the “visual anchor-based MIC distribution method” as an alternative to purely anchor- or distribution-based methods. Using an anchor, they divide a population into three groups, those with important improvement, no important change, and important deterioration. They then plot the distributions of change scores from the target instrument for the three groups using proportional frequencies. A cut-off point is then determined based on these plots, with a goal of reducing possible misclassifications. This method appears to be most appropriate for my goal of determining the minimally important change score for the CALI-HaN. As described by Hendricks et al. (2008), I would consider using a global rating scale with the following categories as the anchor: (1) completely improved, (2) much improved, (3) moderately improved, (4) slightly improved, (5) unchanged, (6) slightly deteriorated, (7) moderately deteriorated, (8) much deteriorated, (9) worse than ever.

8.9. Concluding remarks

In conclusion, in this thesis I have shown that there is a need for an instrument to measure the *experience with* and *impact of* HNL on patients’ HRQoL. Such a tool may be useful in both clinical and research applications to identify the impact of HNL, determine actionable treatment targets, and monitor change over time and in response to interventions. A broad array of HRQoL impacts have been considered and integrated into the CALI-HaN, the first HRQoL PROM designed specifically for use in patients with HNL. By integrating input from patients and clinical providers, we have developed an instrument with strong content validity. Efforts to further validate this scale are underway.

Bibliography

Agarwal, A., Pain, T., Levesque, J. F., Girgis, A., Hoffman, A., Karnon, J., King, M. T., Shah, K. K., Morton, R. L., & HSRAANZ PROMs Special Interest Group (2022). Patient-reported outcome measures (PROMs) to guide clinical care: recommendations and challenges. *The Medical Journal of Australia*, *216*(1), 9–11. https://doi-org/10.5694/mja2.51355

Akashi, M., Teraoka, S., Kakei, Y., Kusumoto, J., Hasegawa, T., Minamikawa, T., Hashikawa, K., & Komori, T. (2018). Computed Tomographic Evaluation of Posttreatment Soft-Tissue Changes by Using a Lymphedema Scoring System in Patients with Oral Cancer. *Lymphatic Research and Biology*, *16*(2), 147–153. https://doi.org/10.1089/lrb.2016.0063

Alamoudi, U., Taylor, B., MacKay, C., Rigby, M. H., Hart, R., Trites, J. R. B., & Taylor, S. M. (2018). Submental liposuction for the management of lymphedema following head and neck cancer treatment: a randomized controlled trial. *Journal of Otolaryngology - Head & Neck Surgery = Le Journal d'oto-rhino-laryngologie et de Chirurgie Cervico-faciale*, *47*(1), 22. https://doi.org/10.1186/s40463-018-0263-1

Alcañiz, M. & Solé-Auró, A. (2018). Feeling good in old age: factors explaining health-related quality of life. *Health and Quality of Life Outcomes,* 16(1), 48. https://doi.org/10.1186/s12955-018-0877-z

Aldrich, M. B., Guilliod, R., Fife, C. E., Maus, E. A., Smith, L., Rasmussen, J. C., & Sevick-Muraca, E. M. (2012). Lymphatic abnormalities in the normal contralateral arms of subjects with breast cancer-related lymphedema as assessed by near-infrared fluorescent imaging. *Biomedical Optics Express*, *3*(6), 1256–1265. https://doi.org/10.1364/BOE.3.001256

Almanasreh, E., Moles, R., & Chen, T.F. (2019). Evaluation of methods used for estimating content validity. *Research in Social and Administrative Pharmacy,* 15(2), 214-21. https://doi.org/10.1016/j.sapharm.2018.03.066

Alterio, D., Marvaso, G., Ferrari, A., Volpe, S., Orecchia, R., & Jereczek-Fossa, B. A. (2019). Modern radiotherapy for head and neck cancer. *Seminars in Oncology*, *46*(3), 233–245. https://doi.org/10.1053/j.seminoncol.2019.07.002

Antunes, B., Harding, R., Higginson, I. J., & EUROIMPACT (2014). Implementing patient-reported outcome measures in palliative care clinical practice: a systematic review of facilitators and barriers. *Palliative medicine*, *28*(2), 158–175. https://doi-org/10.1177/0269216313491619

Arends, C. R., Lindhout, J. E., van der Molen, L., Wilthagen, E. A., van den Brekel, M. W. M., & Stuiver, M. M. (2023). A systematic review of validated assessments methods for head and neck lymphedema. *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*, *280*(6), 2653–2661. https://doi.org/10.1007/s00405-023-07841-0

Arié, A., & Yamamoto, T. (2020). Lymphedema secondary to melanoma treatments: diagnosis, evaluation, and treatments. *Global Health & Medicine*, *2*(4), 227–234. https://doi.org/10.35772/ghm.2020.01022

Arif, R., Marzouki, H. Z., Silver, J. A., Al Thomali, R., Merdad, M., & Sadeghi, N. (2023). Primary prevention of depression in head and neck cancer patients: a scoping 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*, *280*(4), 1547–1554. https://doi-org/10.1007/s00405-022-07783-z

Arrese, L. C., Carrau, R., & Plowman, E. K. (2017). Relationship Between the Eating Assessment Tool-10 and Objective Clinical Ratings of Swallowing Function in Individuals with Head and Neck Cancer. *Dysphagia*, *32*(1), 83–89. https://doi.org/10.1007/s00455-016-9741-7

Arslan, H. H., Ahmadov, A., Cebeci, S., Binar, M., & Karahatay, S. (2016). Life Priorities in Head and Neck Cancer Patients Between Ages of 45 to 65. *The Journal of Craniofacial Surgery*, *27*(4), e398–e401. https://doi.org/10.1097/SCS.0000000000002671

Asaba, K., & Okawa, A. (2021). Moderating effect of sense of coherence on the relationship between symptom distress and health-related quality of life in patients receiving cancer chemotherapy. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *29*(8), 4651–4662. https://doi.org/10.1007/s00520-021-06003-4

Ashley, L., Marti, J., Jones, H., Velikova, G., & Wright, P. (2015). Illness perceptions within 6 months of cancer diagnosis are an independent prospective predictor of health-related quality of life 15 months post-diagnosis. *Psycho-oncology*, *24*(11), 1463–1470. https://doi.org/10.1002/pon.3812

Atkinson, T. M., Schwartz, C. E., Goldstein, L., Garcia, I., Storfer, D. F., Li, Y., Zhang, J., Bochner, B. H., & Rapkin, B. D. (2019). Perceptions of Response Burden Associated with Completion of Patient-Reported Outcome Assessments in Oncology. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *22*(2), 225–230. https://doi.org/10.1016/j.jval.2018.07.875

Audi, R. (2011) *Epistemology: A contemporary introduction to the theory of knowledge*. Routledge Publishing, London. https://doi.org/10/4324/9780203846469

Aulino, J. M., Wulff-Burchfield, E. M., Dietrich, M. S., Ridner, S. H., Niermann, K. J., Deng, J., Rhoten, B. A., Doersam, J. K., Jarrett, L. A., Mannion, K., & Murphy, B. A. (2018). Evaluation of CT Changes in the Head and Neck After Cancer Treatment: Development of a Measurement Tool. *Lymphatic Research and Biology*, *16*(1), 69–74. https://doi.org/10.1089/lrb.2017.0024

Ayestaray, B., Bekara, F., & Andreoletti, J. B. (2013). π-shaped lymphaticovenular anastomosis for head and neck lymphoedema: a preliminary study. *Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS*, *66*(2), 201–206. https://doi.org/10.1016/j.bjps.2012.08.049

Ayre, C. & Scally, A.J. (2014) Critical values for Lawshe's Content Validity Ratio: Revisiting the original methods of calculation. *Measurement and Evaluation in Counseling and Development*, 47(1), 79-86. https://doi.org/10.1177/0748175613513808

Bakas, T., McLennon, S. M., Carpenter, J. S., Buelow, J. M., Otte, J. L., Hanna, K. M., Ellett, M. L., Hadler, K. A., & Welch, J. L. (2012). Systematic review of health-related quality of life models. *Health and Quality of Life Outcomes*, *10*, 134. https://doi.org/10.1186/1477-7525-10-134

Barbera, L., Sutradhar, R., Howell, D., Sussman, J., Seow, H., Dudgeon, D., Atzema, C., Earle, C., Husain, A., Liu, Y., & Krzyzanowska, M. K. (2015). Does routine symptom screening with ESAS decrease ED visits in breast cancer patients undergoing adjuvant chemotherapy? *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *23*(10), 3025–3032. https://doi.org/10.1007/s00520-015-2671-3

Basch, E., Deal, A. M., Dueck, A. C., Scher, H. I., Kris, M. G., Hudis, C., & Schrag, D. (2017). Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. *Journal of the American Medical Association*, *318*(2), 197–198. https://doi.org/10.1001/jama.2017.7156

Basch, E., Spertus, J., Dudley, R. A., Wu, A., Chuahan, C., Cohen, P., Smith, M. L., Black, N., Crawford, A., Christensen, K., Blake, K., & Goertz, C. (2015). Methods for Developing Patient-Reported Outcome-Based Performance Measures (PRO-PMs). *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *18*(4), 493–504. https://doi.org/10.1016/j.jval.2015.02.018

Beelen, L. M., van Dishoeck, A. M., Tsangaris, E., Coriddi, M., Dayan, J. H., Pusic, A. L., Klassen, A., & Vasilic, D. (2021). Patient-Reported Outcome Measures in

Lymphedema: A Systematic Review and COSMIN Analysis. *Annals of Surgical Oncology*, *28*(3), 1656–1668. https://doi.org/10.1245/s10434-020-09346-0

Beeler, W. H., Bellile, E. L., Casper, K. A., Jaworski, E., Burger, N. J., Malloy, K. M., Spector, M. E., Shuman, A. G., Rosko, A., Stucken, C. L., Chinn, S. B., Dragovic, A. F., Chapman, C. H., Owen, D., Jolly, S., Bradford, C. R., Prince, M. E. P., Worden, F. P., Jagsi, R., Mierzwa, M. L., … Swiecicki, P. L. (2020). Patient-reported financial toxicity and adverse medical consequences in head and neck cancer. *Oral Oncology*, *101*, 104521. https://doi.org/10.1016/j.oraloncology.2019.104521

Beisecker, A.E. (1990). Patient power in doctor-patient communication: What do we know. *Health Commun*ication, 2(2), 105-22. https://doi.org/10.1207/s15327027hc0202_4

Belisario, J.S.M., Jamsek, J., Huckvale, K., O'Donoghue, J., Morrison, C.P., Car, J. (2015). Comparison of self-administered survey questionnaire responses collected using mobile apps versus other methods. *Cochrane Database Systematic Reviews,* 7, MR000042. https://doi.org/10.1002/14651858.MR000042.pub2

Benedict, P. A., Kravietz, A., Yang, J., Achlatis, E., Doyle, C., Johnson, A. M., Dion, G. R., & Amin, M. R. (2023). Longitudinal Effects of Base of Tongue Concurrent Chemoradiation Therapy in a Pre-Clinical Model. *The Laryngoscope*, *133*(6), 1455–1461. https://doi-org/10.1002/lary.30393

Benson, T. (2022) Patient Reported Outcomes and Experience: Measuring What we Want from PROMs and PREMs. Springer, Cham, Switzerland. https://doi.org/10.1007/978-3-030-97071-0

Bhangu, S., Provost, F., & Caduff, C. (2023). Introduction to qualitative research methods - Part I. *Perspectives in Clinical Research*, *14*(1), 39–42. https://doi.org/10.4103/picr.picr_253_22

Bigelow, E. O., Blackford, A. L., Eytan, D. F., Eisele, D. W., & Fakhry, C. (2020). Burden of comorbidities is higher among elderly survivors of oropharyngeal cancer compared with controls. *Cancer*, *126*(8), 1793–1803. https://doi.org/10.1002/cncr.32703

Birks, M. & Mills, J. (2022) *Grounded Theory: a practical guide (Third Edition)*. Sage Publishing, Thousand Oaks, CA.

Bjordal, K., Freng, A., Thorvik, J., & Kaasa, S. (1995). Patient self-reported and clinician-rated quality of life in head and neck cancer patients: a cross-sectional study. *European journal of cancer. Part B, Oral Oncology*, *31B* (4), 235–241. https://doi.org/10.1016/0964-1955(95)00010-f

Blane, D., Netuveli, G., & Montgomery, S.M. (2008). Quality of life, health, and physiological status and change at older ages. *Social Science and Medicine,* 66(7), 1579-87. https://doi.org/10.1016/j.socscimed.2007.12.021

Blasco, M. A., Cordero, J., & Dundar, Y. (2020). Chronic Pain Management in Head and Neck Oncology. *Otolaryngologic Clinics of North America*, *53*(5), 865–875. https://doi-org/10.1016/j.otc.2020.05.015

Bliven, B.D., Kaufman, S.E., Spertus J.A. (2001). Electronic collection of health-related quality of life data: validity, time benefits, and patient preference. *Quality of Life Research,* 10(1), 15-21. https://doi.org/10.1023/A:1016740312904

Booth, A., Sutton, A., & Papaioannou, D. (2016) *Systematic Approaches to a Successful Literature Review (2nd edition)*. Sage Publishers, London UK.

Bottomley, A., Aaronson, N. K., & European Organisation for Research and Treatment of Cancer (2007). International perspective on health-related quality-of-life research in cancer clinical trials: the European Organisation for Research and Treatment of Cancer experience. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *25*(32), 5082–5086. https://doi.org/10.1200/JCO.2007.11.3183

Bowman, C., Piedalue, K. A., Baydoun, M., & Carlson, L. E. (2020). The Quality of Life and Psychosocial Implications of Cancer-Related Lower-Extremity Lymphedema: A Systematic Review of the Literature. *Journal of Clinical Medicine*, *9*(10), 3200. https://doi.org/10.3390/jcm9103200

Bradburn, N., Sudman, S., & Wansink, B. (2004). *Asking Questions: The definitive guide to questionnaire design – for market research, political polls, and social and health questionnaires, Revised edition*. San Francisco: Jossey-Bass, A Wiley Imprint.

Bradshaw, C., Atkinson, S., & Doody, O. (2017). Employing a Qualitative Description Approach in Health Care Research. *Global Qualitative Nursing Research*, *4*, 2333393617742282. https://doi-org /10.1177/2333393617742282

Brake, M. K., Jain, L., Hart, R. D., Trites, J. R., Rigby, M., & Taylor, S. M. (2014). Liposuction for Submental Lymphedema Improves Appearance and Self-Perception in the Head and Neck Cancer Patient. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *151*(2), 221–225. https://doi.org/10.1177/0194599814529401

Braun, V. & Clarke, V. (2021). One size fits all? What counts as quality practice in (reflexive) thematic analysis? *Qualitative Research in Psychology*, 18(3), 328-52. https://doi.org/10.1080/14780887.2020.1769238

Braun, V. & Clarke, V. (2019). To saturate or not to saturate? Questioning data saturation as a useful concept for thematic analysis and sample size rationales. *Qualitative Research in Sport, Exercise, and Health*. 13(2), 201-216. https://doi.org/10.1080/2159676x.2019.1704846

Braun, V. & Clarke, V. (2013) *Successful Qualitative Research: A Practical Guide for Beginners.* Sage Publishers, London UK.

Braun, V. & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology,* 3, 77-101. https://doi.org/10.1191/1478088706qp063oa

Broom, A. & Willis, E. (2007) Competing paradigms and health research. In *Researching Health: Qualitative, quantitative, and mixed methods*. Sage Publishers, London UK.

Brown, M. E. L., & Dueñas, A. N. (2019). A Medical Science Educator's Guide to Selecting a Research Paradigm: Building a Basis for Better Research. *Medical Science Educator*, *30*(1), 545–553. https://doi.org/10.1007/s40670-019-00898-9

Bruns, F., Büntzel, J., Mücke, R., Schönekaes, K., Kisters, K., & Micke, O. (2004). Selenium in the treatment of head and neck lymphedema. *Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre*, *13*(4), 185–190. https://doi.org/10.1159/000078313

Bryman, A. (2001). *Social Research Method*. Oxford University Press, Oxford UK.

Bunniss, S., & Kelly, D. R. (2010). Research paradigms in medical education research. *Medical Education*, *44*(4), 358–366. https://doi.org/10.1111/j.1365-2923.2009.03611.x

Bury, M. (1982). Chronic illness as biographical disruption. *Sociology of Health & Illness*, *4*(2), 167–182. https://doi.org/10.1111/1467-9566.ep11339939

Campbell, R., Ju, A., King, M. T., & Rutherford, C. (2022). Perceived benefits and limitations of using patient-reported outcome measures in clinical practice with individual patients: a systematic review of qualitative studies. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *31*(6), 1597–1620. https://doi.org/10.1007/s11136-021-03003-z

Carlsen, B., & Glenton, C. (2011). What about N? A methodological study of sample-size reporting in focus group studies. *BMC Medical Research Methodology*, *11*, 26. https://doi.org/10.1186/1471-2288-11-26

Carlton, J., Peasgood, T., Khan, S., Barber, R., Bostock, J., & Keetharuth, A. D. (2020). An emerging framework for fully incorporating public involvement (PI) into patient-reported outcome measures (PROMs). *Journal of Patient-Reported Outcomes*, *4*(1), 4. https://doi.org/10.1186/s41687-019-0172-8

Carter, J., Huang, H. Q., Armer, J., Carlson, J. W., Lockwood, S., Nolte, S., Kauderer, J., Hutson, A., Walker, J. L., Fleury, A. C., Bonebrake, A., Soper, J. T., Mathews, C., Zivanovic, O., Richards, W. E., Tan, A., Alberts, D. S., Barakat, R. R., & Wenzel, L. B. (2021). GOG 244 - The Lymphedema and Gynecologic cancer (LeG) study: The impact of lower-extremity lymphedema on quality of life, psychological adjustment, physical disability, and function. *Gynecologic Oncology*, *160*(1), 244–251. https://doi.org/10.1016/j.ygyno.2020.10.023

Cella, D. F., Tulsky, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., Silberman, M., Yellen, S. B., Winicour, P., & Brannon, J. (1993). The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *11*(3), 570–579. https://doi.org/10.1200/JCO.1993.11.3.570

Cemal, Y., Jewell, S., Albornoz, C. R., Pusic, A., & Mehrara, B. J. (2013). Systematic review of quality of life and patient reported outcomes in patients with oncologic related lower extremity lymphedema. *Lymphatic Research and Biology*, *11*(1), 14–19. https://doi.org/10.1089/lrb.2012.0015

Chang, C.H. (2007). Patient-reported outcomes measurement and management with innovative methodologies and technologies. *Quality of Life Research,* 16(Suppl 1), 157-66. https://doi.org/10.1007/s11136-007-9196-2

Charmaz, K. (2002). Qualitative interviewing and grounded theory analysis. In J.F. Gubrium & J.A. Holstein (Eds.), *Handbook of interview research: Context and method* (pp. 675-94). Thousand Oaks, CA: Sage.

Charmaz, K. (2014). *Constructing Grounded Theory (Second Edition)*. Sage Publishing, Thousand Oaks, CA.

Chen, A. Y., Frankowski, R., Bishop-Leone, J., Hebert, T., Leyk, S., Lewin, J., & Goepfert, H. (2001). The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. *Archives of Otolaryngology--Head & Neck Surgery*, *127*(7), 870–876. https://doi.org/10-1001/pubs.ArchOtolaryngol.

Chen, Y. P., Chan, A. T. C., Le, Q. T., Blanchard, P., Sun, Y., & Ma, J. (2019). Nasopharyngeal carcinoma. *Lancet (London, England)*, *394*(10192), 64–80. https://doi.org/10.1016/S0140-6736(19)30956-0

Cheng, H., Green, A., Wolpert, M., Deighton, J., & Furnham, A. (2014). Factors influencing adult quality of life: findings from a nationally representative sample in the

UK. *Personality and Individual Differences,* 68, 241-6. https://doi.org/10.1016/j.paid.2014.04.026

Cho, S. F., Rau, K. M., Shao, Y. Y., Yen, C. J., Wu, M. F., Chen, J. S., Chang, C. S., Yeh, S. P., Chiou, T. J., Hsieh, R. K., Lee, M. Y., Sung, Y. C., Lee, K. D., Lai, P. Y., Yu, M. S., Hwang, W. L., & Liu, T. C. (2019). Patients with head and neck cancer may need more intensive pain management to maintain daily functioning: a multi-center study. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *27*(5), 1663–1672. https://doi-org./10.1007/s00520-018-4404-x

Churruca, K., Pomare, C., Ellis, L. A., Long, J. C., Henderson, S. B., Murphy, L. E. D., Leahy, C. J., & Braithwaite, J. (2021). Patient-reported outcome measures (PROMs): A review of generic and condition-specific measures and a discussion of trends and issues. *Health Expectations: An International Journal of Public Participation in Health care and Health Policy*, *24*(4), 1015–1024. https://doi-org/10.1111/hex.13254

Comins, J. D., Brodersen, J., Siersma, V., Jensen, J., Hansen, C. F., & Krogsgaard, M. R. (2021). How to develop a condition-specific PROM. *Scandinavian Journal of Medicine & Science in Sports*, *31*(6), 1216–1224. https://doi.org/10.1111/sms.13868

Connelly, J. E., Philbrick, J. T., Smith, G. R., Jr, Kaiser, D. L., & Wymer, A. (1989). Health perceptions of primary care patients and the influence on health care utilization. *Medical Care*, *27*(3 Suppl), S99–S109. https://doi.org/10.1097/00005650-198903001-00009

Constitution of the World Health Organization. (2005). In: *World Health Organization: Basic Documents. 45th Ed*. Geneva: World Health Organization.

Cook, D. J., Mulrow, C. D., & Haynes, R. B. (1997). Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of Internal Medicine*, *126*(5), 376–380. https://doi.org/10.7326/0003-4819-126-5-199703010-00006

Coran, J. J., Koropeckyj-Cox, T., & Arnold, C. L. (2013). Are physicians and patients in agreement? Exploring dyadic concordance. *Health Education & Behavior: The Official Publication of the Society for Public Health Education*, *40*(5), 603–611. https://doi.org/10.1177/1090198112473102

Cormier, J. N., Askew, R. L., Mungovan, K. S., Xing, Y., Ross, M. I., & Armer, J. M. (2010). Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*, *116*(22), 5138–5149. https://doi.org/10.1002/cncr.25458

Coyne, I.T. (1997). Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries? *Journal of Advanced Nursing*, *26*(3), 623–630. https://doi.org/10.1046/j.1365-2648.1997.t01-25-00999.x

Crary, M. A., Mann, G. D., & Groher, M. E. (2005). Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Archives of Physical Medicine and Rehabilitation*, *86*(8), 1516–1520. https://doi.org/10.1016/j.apmr.2004.11.049

Crosby, R. D., Kolotkin, R. L., & Williams, G. R. (2003). Defining clinically meaningful change in health-related quality of life. *Journal of Clinical Epidemiology*, *56*(5), 395–407. https://doi-org/10.1016/s0895-4356(03)00044-1

Culbertson, M. G., Bennett, K., Kelly, C. M., Sharp, L., & Cahir, C. (2020). The psychosocial determinants of quality of life in breast cancer survivors: a scoping review. *BMC Cancer*, *20*(1), 948. https://doi-org/10.1186/s12885-020-07389-w

Daneshgaran, G., Lo, A. Y., Paik, C. B., Cooper, M. N., Sung, C., Jiao, W., Park, S. Y., Ni, P., Yu, R. P., Vorobyova, I., Jashashvili, T., Hong, Y. K., Kim, G. H., Conti, P. S., Chai, Y., & Wong, A. K. (2019). A Pre-clinical Animal Model of Secondary Head and Neck Lymphedema. *Scientific Reports*, *9*(1), 18264. https://doi.org/10.1038/s41598-019-54201-2

Delon, C., Brown, K. F., Payne, N. W. S., Kotrotsios, Y., Vernon, S., & Shelton, J. (2022). Differences in cancer incidence by broad ethnic group in England, 2013-2017. *British Journal of Cancer*, *126*(12), 1765–1773. https://doi.org/10.1038/s41416-022-01718-5

Deltombe, T., Jamart, J., Recloux, S., Legrand, C., Vandenbroeck, N., Theys, S., & Hanson, P. (2007). Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. *Lymphology*, *40*(1), 26–34.

Deng, J., Dietrich, M. S., Niermann, K. J., Sinard, R. J., Cmelak, A. J., Ridner, S. H., Gilbert, J., & Murphy, B. A. (2021). Refinement and Validation of the Head and Neck Lymphedema and Fibrosis Symptom Inventory. *International Journal of Radiation Oncology, Biology, & Physics*, *109*(3), 747–755. https://doi.org/10.1016/j.ijrobp.2020.10.003

Deng, J., Dietrich, M. S., Ridner, S. H., Fleischer, A. C., Wells, N., & Murphy, B. A. (2016). Preliminary evaluation of reliability and validity of head and neck external lymphedema and fibrosis assessment criteria. *European Journal of Oncology Nursing: The Official Journal of European Oncology Nursing Society*, *22*, 63–70. https://doi.org/10.1016/j.ejon.2016.02.001

Deng, J. & Murphy, B.A. (2016). Lymphedema self-care in patients with head and neck cancer: a qualitative study. *Supportive Care in Cancer*, 24(12), 4961-4970. https://doi.org/10.1007/s00520-016-3356-2

Deng, J., Murphy, B. A., Dietrich, M. S., Sinard, R. J., Mannion, K., & Ridner, S. H. (2016). Differences of symptoms in head and neck cancer patients with and without lymphedema. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *24*(3), 1305–1316. https://doi.org/10.1007/s00520-015-2893-4

Deng, J., Murphy, B. A., Dietrich, M. S., Wells, N., Wallston, K. A., Sinard, R. J., Cmelak, A. J., Gilbert, J., & Ridner, S. H. (2013b). Impact of secondary lymphedema after head and neck cancer treatment on symptoms, functional status, and quality of life. *Head & Neck*, *35*(7), 1026–1035. https://doi.org/10.1002/hed.23084

Deng, J., Murphy, B.A., Niermann, K.J., Sinard, S.J., Cmelak, A.J., Rohde, S.L., Ridner, S.H., & Dietrich, M.S. (2022). Validity testing of the Head and Neck Lymphedema and Fibrosis Symptom Inventory. *Lymphatic Research and Biology*, 20(6), 629-639. https://doi.org/10.1089/lrb.2021.0041

Deng, J., Ridner, S. H., Aulino, J. M., & Murphy, B. A. (2015). Assessment and measurement of head and neck lymphedema: state-of-the-science and future directions. *Oral Oncology*, *51*(5), 431–437. https://doi.org/10.1016/j.oraloncology.2015.01.005

Deng, J., Ridner, S. H., Dietrich, M. S., Wells, N., & Murphy, B. A. (2013a). Assessment of external lymphedema in patients with head and neck cancer: a comparison of four scales. *Oncology Nursing Forum*, *40*(5), 501–506. https://doi.org/10.1188/13.ONF.501-506

Deng, J., Ridner, S. H., Dietrich, M. S., Wells, N., Wallston, K. A., Sinard, R. J., Cmelak, A. J., & Murphy, B. A. (2012). Factors associated with external and internal lymphedema in patients with head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics*, *84*(3), e319–e328. https://doi.org/10.1016/j.ijrobp.2012.04.013

Deng, J., Ridner, S.H., Dietrich, M.S., Wells, N., Wallston, K.A., Sinard, R.J., Cmelak, A.J., & Murphy, B.A. (2012). Prevalence of secondary lymphedema in patient with head and neck cancer. *Journal of Pain and Symptom Management*. 43(2), 244-52. https://doi.org/10.1016/j.jpainsymman.2011.03.019

Deng, J., Ridner, S. H., & Murphy, B. A. (2011). Lymphedema in patients with head and neck cancer. *Oncology Nursing Forum*, *38*(1), E1–E10. https://doi.org/10.1188/11.ONF.E1-E10

Deng, J., Ridner, S. H., Murphy, B. A., & Dietrich, M. S. (2012). Preliminary development of a lymphedema symptom assessment scale for patients with head and neck cancer. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *20*(8), 1911–1918. https://doi.org/10.1007/s00520-011-1294-6

Deng, J., Ridner, S. H., Wells, N., Dietrich, M. S., & Murphy, B. A. (2015). Development and preliminary testing of head and neck cancer related external lymphedema and fibrosis assessment criteria. *European Journal of Oncology Nursing: The Official Journal of European Oncology Nursing Society*, *19*(1), 75–80. https://doi.org/10.1016/j.ejon.2014.07.006

Deng, J., Sinard, R. J., & Murphy, B. (2019). Patient experience of head and neck lymphedema therapy: a qualitative study. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *27*(5), 1811–1823. https://doi.org/10.1007/s00520-018-4428-2

Detmar, S. B., Muller, M. J., Schornagel, J. H., Wever, L. D., & Aaronson, N. K. (2002). Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *Journal of the American Medical Association*, *288*(23), 3027–3034. https://doi-org./10.1001/jama.288.23.3027

deVet, H.C.W., Terwee, C.B., Mokkink, L.B., Knol, D.L. (2018). *Measurement in Medicine*. Cambridge University Press, Cambridge UK.

DeWalt, D. A., Rothrock, N., Yount, S., Stone, A. A., & PROMIS Cooperative Group (2007). Evaluation of item candidates: the PROMIS qualitative item review. *Medical Care*, *45*(5 Suppl 1), S12–S21. https://doi.org/10.1097/01.mlr.0000254567.79743.e2

Dey, I. (1999). Grounding Grounded Theory. Academic Press.

Dijkstra, P. U., Kalk, W. W., & Roodenburg, J. L. (2004). Trismus in head and neck oncology: a systematic review. *Oral Oncology*, *40*(9), 879–889. https://doi.org/10.1016/j.oraloncology.2004.04.003

Di Maio, M., Basch, E., Denis, F., Fallowfield, L. J., Ganz, P. A., Howell, D., Kowalski, C., Perrone, F., Stover, A. M., Sundaresan, P., Warrington, L., Zhang, L., Apostolidis, K., Freeman-Daily, J., Ripamonti, C. I., Santini, D., & ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org (2022). The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, *33*(9), 878–892. https://doi.org/10.1016/j.annonc.2022.04.007

DiSipio, T., Rye, S., Newman, B., & Hayes, S. (2013). Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *The Lancet. Oncology*, *14*(6), 500–515. https://doi.org/10.1016/S1470-2045(13)70076-7

Dixon-Woods, M., Agarwal, S., Jones, D., Young, B., & Sutton, A. (2005). Synthesising qualitative and quantitative evidence: a review of possible methods. *Journal of Health Services Research & Policy*, *10*(1), 45–53. https://doi.org/10.1177/135581960501000110

Doke, K. N., Bowman, L., Shnayder, Y., Shen, X., TenNapel, M., Thomas, S. M., Neupane, P., Yeh, H. W., & Lominska, C. E. (2018). Quantitative clinical outcomes of therapy for head and neck lymphedema. *Advances in Radiation Oncology*, *3*(3), 366–371. https://doi.org/10.1016/j.adro.2018.04.007

Dornan, M., Semple, C., & Moorhead, A. (2022). Experiences and perceptions of social eating for patients living with and beyond head and neck cancer: a qualitative study. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *30*(5), 4129–4137. https://doi-org/10.1007/s00520-022-06853-6

Doyle, L., McCabe, C., Keogh, B., Brady, A., McCann, M. (2020). An overview of the qualitative descriptive design within nursing research. *Journal of Research in Nursing,* 25(5), 443-55. https://doi.org/10.1177/1744987119880234

Driscoll, B., Leonard, L. D., Kovar, A., Billings, J., Tevis, S. E., Kim, S. P., & Cumbler, E. (2022). Surgeon Perceptions of the Integration of Patient-Reported Outcome Measures into Clinical Practice. *The Journal of Surgical Research*, *280*, 486–494. https://doi.org/10.1016/j.jss.2022.07.038

Du, X. L., & Liu, C. C. (2010). Racial/Ethnic disparities in socioeconomic status, diagnosis, treatment and survival among Medicare-insured men and women with head and neck cancer. *Journal of Health Care for the Poor and Underserved*, *21*(3), 913–930. https://doi.org/10.1353/hpu.0.0331

Ebrahim, S. (1995). Clinical and public health perspectives and applications of health-related quality of life measurement. *Social Science and Medicine*, 41(10), 1383-94. https://doi.org/10.1016/0277-9536(95)00116-o

Ekberg, O., Hamdy, S., Woisard, V., Wuttge-Hannig, A., & Ortega, P. (2002). Social and psychological burden of dysphagia: its impact on diagnosis and treatment. *Dysphagia*, *17*(2), 139–146. https://doi.org/10.1007/s00455-001-0113-5

Emmel, N. (2013). *Sampling and choosing cases in qualitative research*. Safe Publishing, London UK.

English Indices of Deprivation 2019. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019. Accessed September 16, 2022.

Eton, D. T., Beebe, T. J., Hagen, P. T., Halyard, M. Y., Montori, V. M., Naessens, J. M., Sloan, J. A., Thompson, C. A., & Wood, D. L. (2014). Harmonizing and consolidating the measurement of patient-reported information at health care institutions: a position statement of the Mayo Clinic. *Patient Related Outcome Measures*, *5*, 7–15. https://doi-org/10.2147/PROM.S55069

Ezeofor, V., Spencer, L. H., Rogers, S. N., Kanatas, A., Lowe, D., Semple, C. J., Hanna, J. R., Yeo, S. T., & Edwards, R. T. (2022). An Economic Evaluation Supported by Qualitative Data About the Patient Concerns Inventory (PCI) versus Standard Treatment Pathway in the Management of Patients with Head and Neck Cancer. *Pharmaco Economics - Open*, *6*(3), 389–403. https://doi.org/10.1007/s41669-021-00320-4

Fadhil, M., Singh, R., Havas, T., & Jacobson, I. (2022). Systematic review of head and neck lymphedema assessment. *Head & Neck*, *44*(10), 2301–2315. https://doi.org/10.1002/hed.27136

Fahy, E., Brooker, R. C., Fleming, J. C., & Patterson, J. M. (2023). A review of unplanned admissions in head and neck cancer patients undergoing oncological treatment. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *31*(6), 328. https://doi.org/10.1007/s00520-023-07770-y

Farnik, M., & Pierzchała, W. A. (2012). Instrument development and evaluation for patient-related outcomes assessments. *Patient Related Outcome Measures*, *3*, 1–7. https://doi.org/10.2147/PROM.S14405

Felce, D., & Perry, J. (1995). Quality of life: its definition and measurement. *Research in Developmental Disabilities*, *16*(1), 51–74. https://doi.org/10.1016/0891-4222(94)00028-8

Ferrans, C.E. (1990). Quality of life: conceptual issues. *Seminars in Oncology Nursing*, 6, 248-54. https://doi.org/10.1016/0749-2081(90)90026-2

Ferrans, C. E., Zerwic, J. J., Wilbur, J. E., & Larson, J. L. (2005). Conceptual model of health-related quality of life. *Journal of Nursing Scholarship: An Official Publication of Sigma Theta Tau International Honor Society of Nursing*, *37*(4), 336–342. https://doi.org/10.1111/j.1547-5069.2005.00058.x

Fingeret, M. C., Hutcheson, K. A., Jensen, K., Yuan, Y., Urbauer, D., & Lewin, J. S. (2013). Associations among speech, eating, and body image concerns for surgical patients with head and neck cancer. *Head & Neck*, *35*(3), 354–360. https://doi.org/10.1002/hed.22980

Finnane, A., Hayes, S. C., Obermair, A., & Janda, M. (2011). Quality of life of women with lower-limb lymphedema following gynecological cancer. *Expert Review of Pharmacoeconomics & Outcomes Research*, *11*(3), 287–297. https://doi.org/10.1586/erp.11.30

Fogg, T. & Wightman, C.W. (2000) *Improving transcription of qualitative research interviews with speech recognition technology*. Paper presented at the Annual Meeting of the American Educational Research Association, New Orleans: U.S. Department of Education Educational Resources Information Center.

Foldi, M.D., Foldi, E., Strossenreuther, R.H.K., & Kubik, S. (2012). *Foldi's Textbook of Lymphology: for Physicians and Lymphedema Therapists, Third ed*. Elsevier Urban & Fischer Verlag, Muchen, Germany.

Forastiere, A. A., Zhang, Q., Weber, R. S., Maor, M. H., Goepfert, H., Pajak, T. F., Morrison, W., Glisson, B., Trotti, A., Ridge, J. A., Thorstad, W., Wagner, H., Ensley, J. F., & Cooper, J. S. (2013). Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *31*(7), 845–852. https://doi.org/10.1200/JCO.2012.43.6097

Francis, J. J., Johnston, M., Robertson, C., Glidewell, L., Entwistle, V., Eccles, M. P., & Grimshaw, J. M. (2010). What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychology & Health*, *25*(10), 1229–1245. https://doi.org/10.1080/08870440903194015

Frost, M. H., Reeve, B. B., Liepa, A. M., Stauffer, J. W., Hays, R. D., & Mayo/FDA Patient-Reported Outcomes Consensus Meeting Group; (2007). What is sufficient evidence for the reliability and validity of patient-reported outcome measures? *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, *10 Suppl 2*, S94–S105. https://doi.org/10.1111/j.1524-4733.2007.00272.x

Fu, M. R., & Kang, Y. (2013). Psychosocial impact of living with cancer-related lymphedema. *Seminars in Oncology Nursing*, *29*(1), 50–60. https://doi.org/10.1016/j.soncn.2012.11.007

Garton, S. & Copeland, F. (2010). "I like this interview; I get cakes and cats!": the effect of prior relationships on interview talk. *Qualitative Research*. 10(5), 533-51.

Gillison, M. L., Chaturvedi, A. K., Anderson, W. F., & Fakhry, C. (2015). Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *33*(29), 3235–3242. https://doi.org/10.1200/JCO.2015.61.6995

Glaser, B.G. (1978). *Theoretical sensitivity: advances in the methodology of grounded theory.* Sociology Press, Mill Valley CA.

Glaser, B.G. & Straus, A.L. (1967). *The discovery of grounded theory: Strategies for qualitative research*. Aldine.

Gold, K. A., Lee, H. Y., & Kim, E. S. (2009). Targeted therapies in squamous cell carcinoma of the head and neck. *Cancer*, *115*(5), 922–935. https://doi.org/10.1002/cncr.24123

Gold, M.R., Patrick, D.L., Torrance, G.W., Fryback, D., Hadorn, D.C., Kamlet, M., et al. (1996). Identifying and valuing outcomes. In Gold, M.R., Russell, L.B., Siegel, J.E., Weinstein, M.C. (eds.) *Cost-effectiveness in health and medicine*. Oxford University Press.

Gopalakrishnan, S., & Ganeshkumar, P. (2013). Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. *Journal of Family Medicine and Primary Care*, *2*(1), 9–14. https://doi.org/10.4103/2249-4863.109934

Gourin, C. G. (2014). Outcomes measurement in patients with head and neck cancer. *Current Oncology Reports*, *16*(3), 376. https://doi.org/10.1007/s11912-013-0376-7

Giuliani, M., McQuestion, M., Jones, J., Papadakos, J., Le, L. W., Alkazaz, N., Cheng, T., Waldron, J., Catton, P., & Ringash, J. (2016). Prevalence and nature of survivorship needs in patients with head and neck cancer. *Head & Neck*, *38*(7), 1097–1103. https://doi.org/10.1002/hed.24411

Grada, A. A., & Phillips, T. J. (2017). Lymphedema: Pathophysiology and clinical manifestations. *Journal of the American Academy of Dermatology*, *77*(6), 1009–1020. https://doi.org/10.1016/j.jaad.2017.03.022

Granström, B., Tiblom Ehrsson, Y., Holmberg, E., Hammerlid, E., Beran, M., Tano, K., Laurell, G., & Swedish Head and Neck Cancer Register (SweHNCR) (2020). Return to work after oropharyngeal cancer treatment-Highlighting a growing working-age population. *Head & Neck*, *42*(8), 1893–1901. https://doi.org/10.1002/hed.26123

Grix, J. (2002). Introducing students to the generic terminology of social research. *Politics*. 22(3), 175-86. https://doi.org/10.1111/1467-9256.00173

Guba, E.G. & Lincoln, Y.S. (1994). Competing paradigms in qualitative research. In NK Denzin & YS Lincoln, editors. *Handbook of Qualitative Research*. Sage Publishing, Thousand Oaks, CA.

Gutierrez, C., Karni, R. J., Naqvi, S., Aldrich, M. B., Zhu, B., Morrow, J. R., Sevick-Muraca, E. M., & Rasmussen, J. C. (2019). Head and Neck Lymphedema: Treatment Response to Single and Multiple Sessions of Advanced Pneumatic Compression Therapy. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *160*(4), 622–626. https://doi.org/10.1177/0194599818823180

Gutiérrez, C., Mayrovitz, H. N., Naqvi, S. H. S., & Karni, R. J. (2020). Longitudinal effects of a novel advanced pneumatic compression device on patient-reported outcomes in the management of cancer-related head and neck lymphedema: A preliminary report. *Head & Neck*, *42*(8), 1791–1799. https://doi.org/10.1002/hed.26110

Handa, S., Pereira, A., & Holmqvist, G. (2023) The rapid decline of happiness: Exploring life satisfaction among young people across the world. *Applied Research in Quality of Life,* 18, 1549-79. https://doi.org/10.1007/s11482-023-10153-4

Hardman, J., Liu, Z., Brady, G., Roe, J., Kerawala, C., Riva, F., Clarke, P., Kim, D., Bhide, S., Nutting, C., Harrington, K., & Paleri, V. (2020). Transoral robotic surgery for recurrent cancers of the upper aerodigestive tract-Systematic review and meta-analysis. *Head & Neck*, *42*(5), 1089–1104. https://doi.org/10.1002/hed.26100

Haugen, T., Senter, J., & Pichardo, P. (2023). Treatment vs Prevention of Head and Neck Cancer: Are We Doing Our Best for Patients? *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *169*(1), 190–191. https://doi.org/10.1177/01945998221116750

Hays, R.D. & Reeve, B.B. (2010). Measurement and modeling of health-related quality of life. In Killewo, J., Heggenhoughen, H.K., & Quah, S.R. (eds.) *Epidemiology and demography in public health.* Academic Press. 195-205.

Hay-Smith, E.J.C., Brown, M., Anderson, L., Treharne, G.J. (2016). Once a clinician, always a clinician: a systematic review to develop a typology of clinician-researcher dual-role experiences in health research with patient participants. *BMC Medical Research Methodology*, 16(95). https://doi.org/10.1186/s12874-016-0203-6

Hennink, M., & Kaiser, B. N. (2022). Sample sizes for saturation in qualitative research: A systematic review of empirical tests. *Social Science & Medicine (1982)*, *292*, 114523. https://doi.org/10.1016/j.socscimed.2021.114523

Hennink, M. M., Kaiser, B. N., & Marconi, V. C. (2017). Code Saturation Versus Meaning Saturation: How Many Interviews Are Enough? *Qualitative Health Research*, *27*(4), 591–608. https://doi.org/10.1177/1049732316665344

Herman, J. M., Narang, A. K., Griffith, K. A., Zalupski, M. M., Reese, J. B., Gearhart, S. L., Azad, N. S., Chan, J., Olsen, L., Efron, J. E., Lawrence, T. S., & Ben-Josef, E.

(2013). The quality-of-life effects of neoadjuvant chemoradiation in locally advanced rectal cancer. *International Journal of Radiation Oncology, Biology, Physics*, *85*(1), e15–e19. https://doi.org/10.1016/j.ijrobp.2012.09.006

Heron, J. & Reason, P. (1997). A participatory inquiry paradigm. *Qualitative Inquiry*. 3(3), 274-94. https://doi.org/10.1177/107780049700300302

Hewitt, M., Greenfield, S., & Stovall, E. (2006). *From Cancer Patient to Cancer Survivor: Lost in Transition*. National Academies Press, 534.

Higginson, I. J., & Carr, A. J. (2001). Measuring quality of life: Using quality of life measures in the clinical setting. *BMJ (Clinical Research Edition)*, *322*(7297), 1297–1300. https://doi.org/10.1136/bmj.322.7297.1297

Hinz, A., Friedrich, M., Kuhnt, S., Zenger, M., & Schulte, T. (2019). The influence of self-efficacy and resilient coping on cancer patients' quality of life. *European Journal of Cancer Care*, *28*(1), e12952. https://doi.org/10.1111/ecc.12952

Holmes, M.M., Stanescu, S., & Bishop, F.L. (2019). The use of measurement systems to support patient self-management of long-term conditions: an overview of opportunities and challenges. *Patient Related Outcome Measures,* 10, 385-94. https://doi.org/10.2147/PROM.S178488

Howell, M., Amir, N., Guha, C., Manera, K., & Tong, A. (2022). The critical role of mixed methods research in developing valid and reliable patient-reported outcome measures. *Methods (San Diego, Calif.)*, *205*, 213–219. https://doi.org/10.1016/j-ymeth.2022.07.012

Høxbroe Michaelsen, S., Grønhøj, C., Høxbroe Michaelsen, J., Friborg, J., & von Buchwald, C. (2017). Quality of life in survivors of oropharyngeal cancer: A systematic review and meta-analysis of 1366 patients. *European Journal of Cancer (Oxford, England: 1990)*, *78*, 91–102. https://doi.org/10.1016/j.ejca.2017.03.006

Hughes, K. L., Williamson, P. R., & Young, B. (2022). In-depth qualitative interviews identified barriers and facilitators that influenced chief investigators' use of core outcome sets in randomised controlled trials. *Journal of Clinical Epidemiology*, *144*, 111–120. https://doi.org/10.1016/j.jclinepi.2021.12.004

Hulbert-Williams, N., Neal, R., Morrison, V., Hood, K., & Wilkinson, C. (2012). Anxiety, depression, and quality of life after cancer diagnosis: what psychosocial variables best predict how patients adjust? *Psycho-oncology*, *21*(8), 857–867. https://doi.org/10.1002/pon.1980

Hull, M. M. (2000). Lymphedema in women treated for breast cancer. *Seminars in Oncology Nursing*, *16*(3), 226–237. https://doi.org/10.1053/sonc.2000.8117

Hunt, M.R., Chan, L.S., Mehta, A. (2011) Transitioning from clinical to qualitative research interviewing. *International Journal of Qualitative Methods*, 10(3), 191-201. https://doi.org/10.1177/160940691101000301

Hunter, C., Fitzpatrick, R., Jenkinson, C., Darlington, A.E., Coutler, A., Forder, J.E., Peter, M. (2015). Perspectives from health, social care, and policy stakeholders on the value of a single self-report outcomes measures across long-term conditions: a qualitative study. *British Medical Journal Open,* 5, e006986. https://doi.org/10.1136/bmjopen-2014-006986

Idler, E. L., & Kasl, S. (1991). Health perceptions and survival: do global evaluations of health status really predict mortality? *Journal of Gerontology*, *46*(2), S55–S65. https://doi.org/10.1093/geronj/46.2.s55

Irvine, A., Drew, P., & Sainsbury, R. (2013). ‘Am I not answering your questions properly?’ Clarification, adequacy, and responsiveness in semi-structured telephone and face-to-face interviews. *Qualitative Research*. 13(1), 87-107. https://doi.org/10.1177/1468794112439086

Jackson, L. K., Ridner, S. H., Deng, J., Bartow, C., Mannion, K., Niermann, K., Gilbert, J., Dietrich, M. S., Cmelak, A. J., & Murphy, B. A. (2016). Internal Lymphedema Correlates with Subjective and Objective Measures of Dysphagia in Head and Neck Cancer Patients. *Journal of Palliative Medicine*, *19*(9), 949–956. https://doi.org/10.1089/jpm.2016.0018

Janardhan, H. P., Jung, R., & Trivedi, C. M. (2023). Lymphatic System in Organ Development, Function, and Regeneration. *Circulation Research*, *132*(9), 1181–1184. https://doi.org/10.1161/CIRCRESAHA.123.322867

Jarvis, C.B., Mackenzie, S.B., & Podsakoff, P.M. (2003). A critical review of construct indicators and measurement model misspecification in marketing and consumer research. *Journal of Consumer Research*, 30(3), 199-218. https://doi.org/10.1086/376806

Jeans, C., Brown, B., Ward, E. C., Vertigan, A. E., Pigott, A. E., Nixon, J. L., & Wratten, C. (2020). Comparing the prevalence, location, and severity of head and neck lymphedema after postoperative radiotherapy for oral cavity cancers and definitive chemoradiotherapy for oropharyngeal, laryngeal, and hypopharyngeal cancers. *Head & Neck*, *42*(11), 3364–3374. https://doi.org/10.1002/hed.26394

Jeans, C., Ward, E. C., Cartmill, B., Vertigan, A. E., Pigott, A. E., Nixon, J. L., & Wratten, C. (2019). Patient perceptions of living with head and neck lymphoedema and the impacts to swallowing, voice and speech function. *European Journal of Cancer Care*, *28*(1), e12894. https://doi.org/10.1111/ecc.12894

Jeans, C., Brown, B., Ward, E. C., Vertigan, A. E., Pigott, A. E., Nixon, J. L., Wratten, C., & Boggess, M. (2023). A Prospective, Longitudinal and Exploratory Study of Head and Neck Lymphoedema and Dysphagia Following Chemoradiotherapy for Head and Neck Cancer. *Dysphagia*, *38*(4), 1059–1071. https://doi.org/10.1007/s00455-022-10526-1

Jeans, C., Ward, E. C., Brown, B., Vertigan, A. E., Pigott, A. E., Nixon, J. L., Wratten, C., & Boggess, M. (2021). Association between external and internal lymphedema and chronic dysphagia following head and neck cancer treatment. *Head & Neck*, *43*(1), 255–267. https://doi.org/10.1002/hed.26484

Jeans, C., Ward, E. C., Cartmill, B., Vertigan, A. E., Pigott, A. E., Nixon, J. L., & Wratten, C. (2019). Patient perceptions of living with head and neck lymphoedema and the impacts to swallowing, voice and speech function. *European Journal of Cancer Care*, *28*(1), e12894. https://doi.org/10.1111/ecc.12894

Jensen, K., Bonde Jensen, A., & Grau, C. (2006). 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: Journal of the European Society for Therapeutic Radiology and Oncology*, *78*(3), 298–305. https://doi.org/10.1016/j.radonc.2006.02.005

Kallio, H., Pietilä, A. M., Johnson, M., & Kangasniemi, M. (2016). Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. *Journal of Advanced Nursing*, *72*(12), 2954–2965. https://doi.org/10.1111/jan.13031

Kamran, S. C., Riaz, N., & Lee, N. (2015). Nasopharyngeal carcinoma. *Surgical Oncology Clinics of North America*, *24*(3), 547–561. https://doi.org/10.1016/j.soc.2015.03.008

Karimi, M., & Brazier, J. (2016). Health, health-related quality of life, and quality of life: What is the difference? *PharmacoEconomics*, 34, 645-49. https://doi.org/10.1007/s40273-016-0389-9

Karri, J., Lachman, L., Hanania, A., Marathe, A., Singh, M., Zacharias, N., Orhurhu, V., Gulati, A., & Abd-Elsayed, A. (2021). Radiotherapy-Specific Chronic Pain Syndromes in the Cancer Population: An Evidence-Based Narrative Review. *Advances in Therapy*, *38*(3), 1425–1446. https://doi-org/10.1007/s12325-021-01640-x

Keen, S., Lomeli-Rodriguez, M., & Joffe, H. (2022). From challenge to opportunity: virtual qualitative research during COVID-19 and beyond. *International Journal of*

Qualitative Methods, *21*, 16094069221105075. https://doi.org/10.1177/16094069221105075

Kendall, K. A., Kosek, S. R., & Tanner, K. (2014). Quality-of-life scores compared to objective measures of swallowing after oropharyngeal chemoradiation. *The Laryngoscope*, *124*(3), 682–687. https://doi.org/10.1002/lary.24344

King, S. N., Dunlap, N. E., Tennant, P. A., & Pitts, T. (2016). Pathophysiology of Radiation-Induced Dysphagia in Head and Neck Cancer. *Dysphagia*, *31*(3), 339–351. https://doi.org/10.1007/s00455-016-9710-1

Klein, J., Livergant, J., & Ringash, J. (2014). Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. *Oral Oncology*, *50*(4), 254–262. https://doi.org/10.1016/j.oraloncology.2014.01.015

Klein, D. E., Winterowd, C. L., Ehrhardt, M. D., Carter, J. C., Khan, O., & Mayes, S. (2020). The relationship of self-compassion and hope with quality of life for individuals with bleeding disorders. *Haemophilia: The Official Journal of the World Federation of Hemophilia*, *26*(3), e66–e73. https://doi.org/10.1111/hae.13959

Klernäs, P., Johnsson, A., Horstmann, V., Kristjanson, L. J., & Johansson, K. (2015). Lymphedema Quality of Life Inventory (LyQLI)-Development and investigation of validity and reliability. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *24*(2), 427–439. https://doi.org/10.1007/s11136-014-0783-8

Krebbers, I., Pilz, W., Vanbelle, S., Verdonschot, R. J. C. G., & Baijens, L. W. J. (2023). Affective Symptoms and Oropharyngeal Dysphagia in Head-and-Neck Cancer Patients: A Systematic Review. *Dysphagia*, *38*(1), 127–144. https://doi.org/10.1007/s00455-022-10484-8

Lango, M. N. (2009). Multimodal treatment for head and neck cancer. *The Surgical Clinics of North America*, *89*(1), 43–viii. https://doi.org/10.1016/j.suc.2008.09.018

Lathen, L. & Laestadius, L. (2021). Reflections on online focus group research with low socio-economic status African American adults during COVID-19. *International Journal of Qualitative Methodology*. 20, 1-10. https://doi.org/10.1177/16094069211021713

Lawshe, CH. (1975). A quantitative approach to content validity. *Personnel Psychology*, 28, 563-75. https://doi.org/10.1111/j.1744-6570.1975.tb01393.x

Lechner, M., Liu, J., Masterson, L., & Fenton, T. R. (2022). HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nature reviews. Clinical Oncology*, *19*(5), 306–327. https://doi.org/10.1038/s41571-022-00603-7

Lee, B.B., Rockson, S.G., & Bergan, J. (Eds.) (2018). *Lymphedema- a concise compendium of theory and practice, Second edition*. Springer, New York, NY.

Lenze, N. R., Bensen, J. T., Farnan, L., Sheth, S., Zevallos, J. P., Yarbrough, W. G., & Zanation, A. M. (2022). Association of self-reported financial burden with quality of life and oncologic outcomes in head and neck cancer. *Head & Neck*, *44*(2), 412–419. https://doi.org/10.1002/hed.26934

Lewin, J.S., Hutcheson, K., Barringer, D., & Smith, B.G. (2010). Preliminary experience with head and neck lymphoedema and swallowing function in patients treated for head and neck cancer. *Perspective on Swallowing and Swallowing Disorders (Dysphagia)*, 19(2), 45-52. https://doi.org/10.1044/sasd19.2.45

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical research Edition)*, *339*, b2700. https://doi.org/10.1136/bmj.b2700

Licqurish, S. M., Cook, O. Y., Pattuwage, L. P., Saunders, C., Jefford, M., Koczwara, B., Johnson, C. E., & Emery, J. D. (2019). Tools to facilitate communication during physician-patient consultations in cancer care: An overview of systematic reviews. *CA: a Cancer Journal for Clinicians*, *69*(6), 497–520. https://doi.org/10.3322/caac.21573

Lin, B. M., Starmer, H. M., & Gourin, C. G. (2012). The relationship between depressive symptoms, quality of life, and swallowing function in head and neck cancer patients 1 year after definitive therapy. *The Laryngoscope*, *122*(7), 1518–1525. https://doi.org/10.1002/lary.23312

List, M. A., & Bilir, S. P. (2004). Functional outcomes in head and neck cancer. *Seminars in Radiation Oncology*, *14*(2), 178–189. https://doi.org/10.1053/j.semradonc.2003.12.008

Little, M., Schipper, M., Feng, F. Y., Vineberg, K., Cornwall, C., Murdoch-Kinch, C. A., & Eisbruch, A. (2012). Reducing xerostomia after chemo-IMRT for head-and-neck cancer: beyond sparing the parotid glands. *International Journal of Radiation Oncology, Biology, Physics*, *83*(3), 1007–1014. https://doi.org/10.1016/j.ijrobp.2011.09.004

Lobe, B., Morgan, D., Hoffman, K.A. (2020). Qualitative data collection in an era of social distancing. *International Journal of Qualitative Methodology*. 19, 1-8. https://doi.org/10.1177/1609406920937875

Lombi, L., Alfieri, S., & Brunelli, C. (2023). 'Why should I fill out this questionnaire?' A qualitative study of cancer patients' perspectives on the integration of e-PROMs in routine clinical care. *European Journal of Oncology Nursing: the Official Journal of the European Oncology Nursing Society*, *63*, 102283. https://doi.org/10.1016/j.ejon.2023.102283

Lu, L., O'Sullivan, E., & Sharp, L. (2019). Cancer-related financial hardship among head and neck cancer survivors: Risk factors and associations with health-related quality of life. *Psycho-oncology*, *28*(4), 863–871. https://doi.org/10.1002/pon.5034

Mace, R. A., Doorley, J., Bakhshaie, J., Cohen, J. E., & Vranceanu, A. M. (2021). Psychological resiliency explains the relationship between emotional distress and quality of life in neurofibromatosis. *Journal of Neuro-oncology*, *155*(2), 125–132. https://doi.org/10.1007/s11060-021-03852-1

Machtay, M., Moughan, J., Trotti, A., Garden, A. S., Weber, R. S., Cooper, J. S., Forastiere, A., & Ang, K. K. (2008). Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *26*(21), 3582–3589. https://doi.org/10.1200/JCO.2007.14.8841

Mady, L. J., Lyu, L., Owoc, M. S., Peddada, S. D., Thomas, T. H., Sabik, L. M., Johnson, J. T., & Nilsen, M. L. (2019). Understanding financial toxicity in head and neck cancer survivors. *Oral Oncology*, *95*, 187–193. https://doi.org/10.1016/j.oraloncology.2019.06.023

Malterud, K. (2016). Theory and interpretation in qualitative studies from general practice: Why and how? *Scandinavian Journal of Public Health*, *44*(2), 120–129. https://doi.org/10.1177/1403494815621181

Martino, R., Beaton, D., & Diamant, N. E. (2010). Perceptions of psychological issues related to dysphagia differ in acute and chronic patients. *Dysphagia*, *25*(1), 26–34. https://doi.org/10.1007/s00455-009-9225-0

Matheson, J.L. (2007). The voice transcription technique: use of voice recognition software to transcribe digital interview data in qualitative research. *The Qualitative Report*. 12(4), 547-60. https://doi.org/10.46743/2160-3715/2007.1611

Maurer, J., Hipp, M., Schäfer, C., & Kölbl, O. (2011). Dysphagia. Impact on quality of life after radio(chemo)therapy of head and neck cancer. *Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft*, *187*(11), 744–749. https://doi.org/10.1007/s00066-011-2275-x

Mayrovitz, H. N., Ryan, S., & Hartman, J. M. (2018). Usability of advanced pneumatic compression to treat cancer-related head and neck lymphedema: A feasibility study. *Head & Neck*, *40*(1), 137–143. https://doi.org/10.1002/hed.24995

Mazariego, C., Jefford, M., Chan, R. J., Roberts, N., Millar, L., Anazodo, A., Hayes, S., Brown, B., Saunders, C., Webber, K., Vardy, J., Girgis, A., Koczwara, B., & COSA PRO Working Group (2022). Priority recommendations for the implementation of patient-reported outcomes in clinical cancer care: a Delphi study. *Journal of Cancer Survivorship: Research and Practice*, *16*(1), 33–43. https://doi.org/10.1007/s11764-021-01135-2

McDowell, L., Bressel, M., King, M.T., Corry, J., Kenny, L., Porceddu, S., Wratten, C., Macann, A., Jackson, J.E., & Rischin, D. (2023). Patient-Reported Symptom Severity, Health-Related Quality of Life, and Emotional Distress Trajectories During and After Radiation Therapy for Human Papillomavirus-Associated Oropharyngeal Cancer: A TROG 12.01 Secondary Analysis. *International Journal of Radiation Oncology, Biology, Physics*. 116(5), 1110-1125. https://doi/org/10.1016/j.ijrobp.2023.02.041

McDowell, L., Casswell, G., Bressel, M., Drosdowsky, A., Rischin, D., Coleman, A., Shrestha, S., D'Costa, I., Fua, T., Tiong, A., Liu, C., & Gough, K. (2021). Symptom burden, quality of life, functioning and emotional distress in survivors of human papillomavirus associated oropharyngeal cancer: An Australian cohort. *Oral Oncology*, *122*, 105560. https://doi.org/10.1016/j.oraloncology.2021.105560

McGarvey, A. C., Osmotherly, P. G., Hoffman, G. R., & Chiarelli, P. E. (2014). Lymphoedema following treatment for head and neck cancer: impact on patients, and beliefs of health professionals. *European Journal of Cancer Care*, *23*(3), 317–327. https://doi.org/10.1111/ecc.12134

McKenna, S.P. (2011). Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. *BMC Medicine*, *9*, 86. https://doi.org/10.1186/1741-7015-9-86

McKenna, S.P. & Doward, L.C. (2004) The needs-based approach to quality of life assessment. Value in Health, 7(s1), s1-3. https://doi.org/10.1111/j.1524-4733.2004.7s101.x

Mehanna, H.M. & Morton, R.P. (2006). Deterioration in quality-of-life of late (10-year) survivors of head and neck cancer. *Clinical Otolaryngology*. (3), 204-211. https://doi.org/10.1111/j.1749-4486.2006.01188.x

Mercieca-Bebber, R., King, M. T., Calvert, M. J., Stockler, M. R., & Friedlander, M. (2018). The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Related Outcome Measures*, *9*, 353–367. https://doi.org/10.2147/PROM.S156279

Messmer, M. B., Thomsen, A., Kirste, S., Becker, G., & Momm, F. (2011). Xerostomia after radiotherapy in the head & neck area: long-term observations. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, *98*(1), 48–50. https://doi.org/10.1016/j.radonc.2010.10.013

Michelotti, A., Invernizzi, M., Lopez, G., Lorenzini, D., Nesa, F., De Sire, A., & Fusco, N. (2019). Tackling the diversity of breast cancer related lymphedema: Perspectives on diagnosis, risk assessment, and clinical management. *Breast (Edinburgh, Scotland)*, *44*, 15–23. https://doi.org/10.1016/j.breast.2018.12.009

Micke, O., Bruns, F., Mücke, R., Schäfer, U., Glatzel, M., DeVries, A. F., Schönekaes, K., Kisters, K., & Büntzel, J. (2003). Selenium in the treatment of radiation-associated secondary lymphedema. *International Journal of Radiation Oncology, Biology, Physics*, *56*(1), 40–49. https://doi.org/10.1016/s0360-3016(02)04390-0

Miller, G. A. (1994). The magical number seven, plus or minus two: some limits on our capacity for processing information. 1956. *Psychological Review*, *101*(2), 343–352. https://doi.org/10.1037/0033-295x.101.2.343

Minasian, L. M., O'Mara, A. M., Reeve, B. B., Denicoff, A. M., Kelaghan, J., Rowland, J. H., Trimble, E. L., & National Cancer Institute (2007). Health-related quality of life and symptom management research sponsored by the National Cancer Institute. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *25*(32), 5128–5132. https://doi.org/10.1200/JCO.2007.12.6672

Mirabile, A., Airoldi, M., Ripamonti, C., Bolner, A., Murphy, B., Russi, E., Numico, G., Licitra, L., & Bossi, P. (2016). Pain management in head and neck cancer patients undergoing chemo-radiotherapy: Clinical practical recommendations. *Critical Reviews in Oncology/hematology*, *99*, 100–106. https://doi-org/10.1016/j.critrevonc.2015.11.010

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. https://doi.org/10.1371/journal.pmed.1000097

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., Bouter, L. M., & de Vet, H. C. (2010). The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *19*(4), 539–549. https://doi.org/10.1007/s11136-010-9606-8

Mokkink, L. B., de Vet, H. C. W., Prinsen, C. A. C., Patrick, D. L., Alonso, J., Bouter, L. M., & Terwee, C. B. (2018). COSMIN Risk of Bias checklist for systematic reviews of

Patient-Reported Outcome Measures. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *27*(5), 1171–1179. https://doi.org/10.1007/s11136-017-1765-4

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., Bouter, L. M., & de Vet, H. C. (2010a). 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), 737–745. https://doi.org/10.1016/j.jclinepi.2010.02.006

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., Bouter, L. M., & de Vet, H. C. (2010b). 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), 737–745. https://doi.org/10.1016/j.jclinepi.2010.02.006

Moreno, A. C., Frank, S. J., Garden, A. S., Rosenthal, D. I., Fuller, C. D., Gunn, G. B., Reddy, J. P., Morrison, W. H., Williamson, T. D., Holliday, E. B., Phan, J., & Blanchard, P. (2019). Intensity modulated proton therapy (IMPT) - The future of IMRT for head and neck cancer. *Oral Oncology*, *88*, 66–74. https://doi.org/10.1016/j.oraloncology.2018.11.015

Morse, J.M. (1995). The significance of saturation. *Qualitative Health Research.* 5: 147-9. https://doi.org/10.1177/104973239500500201

Mortensen, H. R., Jensen, K., & Grau, C. (2013). Aspiration pneumonia in patients treated with radiotherapy for head and neck cancer. *Acta Oncologica (Stockholm, Sweden)*, *52*(2), 270–276. https://doi-org/10.3109/0284186X.2012.742205

Mullan, L. J., Blackburn, N. E., Gracey, J., Dunwoody, L., Lorimer, J., & Semple, C. J. (2023). Evaluating the effects of lymphoedema management strategies on functional status and health-related quality of life following treatment for head and neck cancer: a systematic review. *Journal of Cancer Survivorship: Research and Practice*, https://doi.org/10.1007/s11764-023-01453-7 Advance online publication.

Munn, L. L., & Padera, T. P. (2014). Imaging the lymphatic system. *Microvascular Research*, *96*, 55–63. https://doi.org/10.1016/j.mvr.2014.06.006

Murphy, B. A., & Gilbert, J. (2009). Dysphagia in head and neck cancer patients treated with radiation: assessment, sequelae, and rehabilitation. *Seminars in Radiation Oncology*, *19*(1), 35–42. https://doi.org/10.1016/j.semradonc.2008.09.007

Murphy, B. A., Gilbert, J., & Ridner, S. H. (2007). Systemic and global toxicities of head and neck treatment. *Expert Review of Anticancer Therapy*, *7*(7), 1043–1053. https://doi.org/10.1586/14737140.7.7.1043

Murphy, B.A. & Ridner, S. (2010). Late-effect laryngeal oedema/lymphoedema. *Journal of Lymphoedema*, 5(2), 92-3.

Murphy, B. A., Ridner, S., Wells, N., & Dietrich, M. (2007). Quality of life research in head and neck cancer: a review of the current state of the science. *Critical Reviews in Oncology/Hematology*, *62*(3), 251–267. https://doi.org/10.1016/j.critrevonc.2006.07.005

Nachalon, Y., Nativ-Zeltzer, N., Evangelista, L. M., Dhar, S. I., Lin, S. J., Shen, S. C., & Belafsky, P. C. (2021). Cervical Fibrosis as a Predictor of Dysphagia. *The Laryngoscope*, *131*(3), 548–552. https://doi.org/10.1002/lary.28880

Nagel, T. H., Chang, B. A., & Hinni, M. L. (2022). Robotic vs. transoral laser surgery of malignant oropharyngeal tumors-what is best for the patient? A contemporary review. Robotische vs. transorale Laserchirurgie maligner oropharyngealer Tumoren – was ist für den Patienten am besten? Eine aktuelle Übersicht. *HNO*, *70*(5), 371–379. https://doi.org/10.1007/s00106-022-01165-x

National Institute on Health and Care Research. (2024). Supporting patient and public involvement in research. https://www.nihr.ac.uk/explore-nihr/campaigns/supporting-patient-and-public-involvement-in-research.htm.

Nayak, S. G., Pai, M. S., & George, L. S. (2019). Quality of life of patients with head and neck cancer: A mixed method study. *Journal of Cancer Research and Therapeutics*, *15*(3), 638–644. https://doi.org/10.4103/jcrt.JCRT_1123_16

Neergaard, M. A., Olesen, F., Andersen, R. S., & Sondergaard, J. (2009). Qualitative description - the poor cousin of health research?. *BMC Medical Research Methodology*, *9*, 52. https://doi.org/10.1186/1471-2288-9-52

Ngai, F.W. (2019). Relationships between menopausal symptoms, sense of coherence, coping strategies, and quality of life. *Menopause*. 26(7), 758-764. https://doi.org/10.1097/GME.0000000000001299

Nguyen, N. P., Frank, C., Moltz, C. C., Vos, P., Smith, H. J., Karlsson, U., Dutta, S., Midyett, A., Barloon, J., & Sallah, S. (2005). Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics*, *61*(3), 772–778. https://doi.org/10.1016/j.ijrobp.2004.06.017

Nixon, J. L., Pigott, A. E., Cartmill, B., Turner, J., Fleming, J., & Porceddu, S. V. (2018). A mixed methods examination of distress and person-centred experience of head and neck lymphoedema. *Oral Oncology*, *83*, 18–24. https://doi.org/10.1016/j.oraloncology.2018.05.025

Nixon, J., Purcell, A., Fleming, J., McCann, A., & Porceddu, S. (2014). Pilot study of an assessment tool for measuring head and neck lymphoedema. *British Journal of Community Nursing*, *Suppl*, S6–S11. https://doi.org/10.12968/bjcn.2014.19.Sup4.S6

Nund, R. L., Ward, E. C., Scarinci, N. A., Cartmill, B., Kuipers, P., & Porceddu, S. V. (2014). Survivors' experiences of dysphagia-related services following head and neck cancer: implications for clinical practice. *International Journal of Language & Communication Disorders*, *49*(3), 354–363. https://doi.org/10.1111/1460-6984.12071

Nutting, C. M., Morden, J. P., Harrington, K. J., Urbano, T. G., Bhide, S. A., Clark, C., Miles, E. A., Miah, A. B., Newbold, K., Tanay, M., Adab, F., Jefferies, S. J., Scrase, C., Yap, B. K., A'Hern, R. P., Sydenham, M. A., Emson, M., Hall, E., & PARSPORT trial management group (2011). Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *The Lancet. Oncology*, *12*(2), 127–136. https://doi.org/10.1016/s1470-2045(10)70290-4

O’Brien, B.C., Harris, I.B., Beckman, T.J., Reed, D.A., Cook, D.A. (2014) Standards for Reporting Qualitative Research: A Synthesis of Recommendations. *Academic Medicine*, 89(9), 1245-1251 https://doi.org/10.1097/ACM.0000000000000388

Ojo, B., Genden, E. M., Teng, M. S., Milbury, K., Misiukiewicz, K. J., & Badr, H. (2012). A systematic review of head and neck cancer quality of life assessment instruments. *Oral Oncology*, *48*(10), 923–937. https://doi.org/10.1016/j.oraloncology.2012.03.025

Ozdemir, K., Keser, I., Duzlu, M., Erpolat, O. P., Saranli, U., & Tutar, H. (2021). The Effects of Clinical and Home-based Physiotherapy Programs in Secondary Head and Neck Lymphedema. *The Laryngoscope*, *131*(5), E1550–E1557. https://doi.org/10.1002/lary.29205

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research Edition)*, *372*, n71. https://doi.org/10.1136/bmj.n71.

Pan, W. R., Suami, H., & Taylor, G. I. (2008). Lymphatic drainage of the superficial tissues of the head and neck: anatomical study and clinical implications. *Plastic and Reconstructive Surgery*, *121*(5), 1614–1624. https://doi.org/10.1097/PRS.0b013e31816aa072

Paramanandam, V. S., Lee, M. J., Kilbreath, S. L., & Dylke, E. S. (2021). Self-reported questionnaires for lymphoedema: a systematic review of measurement properties using

COSMIN framework. *Acta Oncologica (Stockholm, Sweden)*, *60*(3), 379–391. https://doi.org/10.1080/0284186X.2020.1862422

Patient-Centered Outcomes Research Institute. (April 24, 2023). The value of Engagement. https://www.pcori.org/engagement/value-engagement

Patterson, J. M., Hildreth, A., & Wilson, J. A. (2007). Measuring edema in irradiated head and neck cancer patients. *The Annals of Otology, Rhinology, and Laryngology*, *116*(8), 559–564. https://doi.org/10.1177/000348940711600801

Patterson, J.M., Lu, L., Watson, L.J., Harding, S., Ness, A.R., Thomas, S., Waylen, A., Pring, M., Waterboer, T., & Sharp, L. (2022). Associations between markers of social functioning and depression and quality of life in survivors of head and neck cancer: Findings from the Head and Neck Cancer 5000 study. *Psychooncology*. 31(3), 478-485. https://doi.org/10.1002/pon.5830

Patton, M.Q. (2015). *Qualitative research & evaluation methods: integrating theory and practice, 4th Edition*. Sage Publications, Thousand Oaks, CA.

Payne, A., Horne, A., Bayman, N., Blackhall, F., Bostock, L., Chan, C., Coote, J., Eaton, M., Fenemore, J., Gomes, F., Halkyard, E., Harris, M., Lindsay, C., McEntee, D., Neal, H., Pemberton, L., Sheikh, H., Woolf, D., Price, J., Yorke, J., … Faivre-Finn, C. (2023). Patient and clinician-reported experiences of using electronic patient reported outcome measures (ePROMs) as part of routine cancer care. *Journal of Patient-reported Outcomes*, *7*(1), 42. https://doi.org/10.1186/s41687-023-00544-4

Peasgood, T., Mukuria, C., Carlton, J., Connell, J., Brazier, J. (2021). Criteria for item selection for a preference-based measure for use in economic evaluation. *Quality of Life Research*;30(5), 1425-1432. https://doi.org/10.1007/s11136-020-02718-9

Pedersen, A., Wilson, J., McColl, E., Carding, P., & Patterson, J. (2016). Swallowing outcome measures in head and neck cancer--How do they compare? *Oral Oncology*, *52*, 104–108. https://doi.org/10.1016/j.oraloncology.2015.10.015

Pezdirec, M., Strojan, P., & Boltezar, I. H. (2019). Swallowing disorders after treatment for head and neck cancer. *Radiology and Oncology*, *53*(2), 225–230. https://doi.org/10.2478/raon-2019-0028

Piso, D. U., Eckardt, A., Liebermann, A., & Gehrke, A. (2002). Reproducibility of sonographic soft-tissue measurement of the head and neck. *American Journal of Physical Medicine & Rehabilitation*, *81*(1), 8–12. https://doi.org/10.1097/00002060-200201000-00003

Piso, D. U., Eckardt, A., Liebermann, A., Gutenbrunner, C., Schäfer, P., & Gehrke, A. (2001). Early rehabilitation of head-neck edema after curative surgery for orofacial tumors. *American Journal of Physical Medicine & Rehabilitation*, *80*(4), 261–269. https://doi.org/10.1097/00002060-200104000-00006

PUBMED. https://pubmed.ncbi.nlm.nih.gov/?term=ePROMs. Accessed 6 December, 2023.

Purcell, A., Nixon, J., Fleming, J., McCann, A., & Porceddu, S. (2016). Measuring head and neck lymphedema: The "ALOHA" trial. *Head & Neck*, *38*(1), 79–84. https://doi.org/10.1002/hed.23853

Pusic, A. L., Cemal, Y., Albornoz, C., Klassen, A., Cano, S., Sulimanoff, I., Hernandez, M., Massey, M., Cordeiro, P., Morrow, M., & Mehrara, B. (2013). Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. *Journal of Cancer Survivorship: Research and Practice*, *7*(1), 83–92. https://doi.org/10.1007/s11764-012-0247-5

Queija, D. D. S., Dedivitis, R. A., Arakawa-Sugueno, L., de Castro, M. A. F., Chamma, B. M., Kulcsar, M. A. V., & de Matos, L. L. (2020). Cervicofacial and Pharyngolaryngeal Lymphedema and Deglutition After Head and Neck Cancer Treatment. *Dysphagia*, *35*(3), 479–491. https://doi.org/10.1007/s00455-019-10053-6

Rathod, S., Livergant, J., Klein, J., Witterick, I., & Ringash, J. (2015). A systematic review of quality of life in head and neck cancer treated with surgery with or without adjuvant treatment. *Oral Oncology*, *51*(10), 888–900. https://doi.org/10.1016/j.oraloncology.2015.07.002

Recinos, P.F., Dunphy C.J., Thompson N., Schuschu J., Urchek J.L., & Katzan I.L. (2017). Patient satisfaction with collection of patient-reported outcome measures in routine care. *Advances in Therapy*, 34, 452-65. https://doi.org/10.1007/s12325-016-0463-x

Remick, J. S., Kowalski, E., Samanta, S., Choi, S., Palmer, J. D., & Mishra, M. V. (2020). Health-Related Quality of Life and Patient-Reported Outcomes in Radiation Oncology Clinical Trials. *Current Treatment Options in Oncology*, *21*(11), 87. https://doi.org/10.1007/s11864-020-00782-4

Rettig, E. M., & D'Souza, G. (2015). Epidemiology of head and neck cancer. *Surgical Oncology Clinics of North America*, *24*(3), 379–396. https://doi.org/10.1016/j.soc.2015.03.001

Ridner, S. H., Deng, J., Doersam, J. K., & Dietrich, M. S. (2021). Lymphedema Symptom Intensity and Distress Surveys-Truncal and Head and Neck, Version 2.0. *Lymphatic Research and Biology*, *19*(3), 240–248. https://doi.org/10.1089/lrb.2020.0071

Ridner, S. H., Dietrich, M. S., Deng, J., Ettema, S. L., & Murphy, B. (2021). Advanced pneumatic compression for treatment of lymphedema of the head and neck: a randomized wait-list controlled trial. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *29*(2), 795–803. https://doi.org/10.1007/s00520-020-05540-8

Ridner, S. H., Dietrich, M. S., Niermann, K., Cmelak, A., Mannion, K., & Murphy, B. (2016). A Prospective Study of the Lymphedema and Fibrosis Continuum in Patients with Head and Neck Cancer. *Lymphatic Research and Biology*, *14*(4), 198–205. https://doi.org/10.1089/lrb.2016.0001

Ringash, J., Bernstein, L. J., Devins, G., Dunphy, C., Giuliani, M., Martino, R., & McEwen, S. (2018). Head and Neck Cancer Survivorship: Learning the Needs, Meeting the Needs. *Seminars in Radiation Oncology*, *28*(1), 64–74. https://doi.org/10.1016/j.semradonc.2017.08.008

Rischin, D., Harrington, K.J., Greil, R., Soulieres, D., Tahara, M., de Castro, G., Jr, Psyrri, A., Brana, I., Neupane, P., Bratland, A., Fuereder, T., Hughes, B.G.M., Mesia, R., Ngamphaiboon, N., Rordorf, T., Ishak, W.Z.W., Hong, R.L., Mendoza, R.G., Jia, L., Chirovsky, D., … Burtness, B. (2022). Pembrolizumab alone or with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma: Health-related quality-of-life results from KEYNOTE-048. *Oral Oncology*. 128, 105815. https://doi.org/10.1016/j.oraloncology.2022.105815

Robert Graham Center. Social Deprivation Index (SDI). 2018.

Roberts, N.A., Alexander, K., Wyld, D., Janda, M. (2019). What is needed by staff to implement PROMs into routine oncology care? A qualitative study with the multi-disciplinary team. *European Journal of Cancer Care,* 28(6), e13167. https://doi.org/10.1111/ecc.13167

Rockson, S. G., Keeley, V., Kilbreath, S., Szuba, A., & Towers, A. (2019). Cancer-associated secondary lymphoedema. *Nature Reviews. Disease Primers*, *5*(1), 22. https://doi.org/10.1038/s41572-019-0072-5

Rogers, S. N., El-Sheikha, J., & Lowe, D. (2009). The development of a Patients Concerns Inventory (PCI) to help reveal patients concerns in the head and neck clinic. *Oral Oncology*, *45*(7), 555–561. https://doi.org/10.1016/j.oraloncology.2008.09.004

Rogers, S.N., Gwanne, S., Lowe, D., Humphris, G., Yueh, B., & Weymuller, E. A., Jr (2002). The addition of mood and anxiety domains to the University of Washington quality of life scale. *Head & Neck*, *24*(6), 521–529. https://doi.org/10.1002/hed.10106

Rogers, S.N., Lowe, D., Yueh, B., & Weymuller, E. A., Jr (2010). The physical function and social-emotional function subscales of the University of Washington Quality of Life Questionnaire. *Archives of Otolaryngology--Head & Neck Surgery*, *136*(4), 352–357. https://doi.org/10.1001/archoto.2010.32

Rogers, S.N., Semple, C., Humphris, G. M., Lowe, D., & Kanatas, A. (2020). Using a patient prompt list to raise concerns in oncology clinics does not necessarily lead to longer consultations. *The British Journal of Oral & Maxillofacial Surgery*, *58*(9), 1164–1171. https://doi.org/10.1016/j.bjoms.2020.08.035

Roick, J., Danker, H., Dietz, A., Papsdorf, K., & Singer, S. (2020). Predictors of changes in quality of life in head and neck cancer patients: a prospective study over a 6-month period. *European Archives in Otorhinolaryngology*. 277(2), 559-567. https://doi.org/10.1007/s00405-019-05695-z

Roiha, A. & Iikkanen, P. (2022). The salience of a prior relationship between researcher and participants: reflecting on acquaintance interviews. *Research Methods in Applied Linguistics*. 1(1), 100003. https://doi.org/10.1016/j.rmal.2021.100003

Rothrock, N. E., Kaiser, K. A., & Cella, D. (2011). Developing a valid patient-reported outcome measure. *Clinical Pharmacology and Therapeutics*, *90*(5), 737–742. https://doi.org/10.1038/clpt.2011.195

Rutherford, C., King, M. T., Smith, D. P., Costa, D. S., Tait, M. A., Patel, M. I., & NMIBC-SI Working Group (2017). Psychometric Evaluation of a Patient-Reported Symptom Index for Nonmuscle Invasive Bladder Cancer: Field Testing Protocol. *JMIR Research Protocols*, *6*(11), e216. https://doi.org/10.2196/resprot.8761

Rylands, J., Lowe, D., & Rogers, S. N. (2016). Influence of deprivation on health-related quality of life of patients with cancer of the head and neck in Merseyside and Cheshire. *The British Journal of Oral & Maxillofacial Surgery*, *54*(6), 669–676. https://doi.org/10.1016/j.bjoms.2016.03.030

Sandelowski, M. (2000). Whatever happened to qualitative description? *Research in Nursing & Health,* 23, 334-40. https://doi.org/10.1002/1098-240x(200008)23:4<334::aid-nur9>3.0.co;2-g

Sandelowski, M. (2010). What's in a name? Qualitative description revisited. *Research in Nursing & Health*, *33*(1), 77–84. https://doi.org/10.1002/nur.20362

Scoggins, J. F., & Patrick, D. L. (2009). The use of patient-reported outcomes instruments in registered clinical trials: evidence from ClinicalTrials.gov. *Contemporary Clinical Trials*, *30*(4), 289–292. https://doi.org/10.1016/j.cct.2009.02.005

Semple, C. J., Dunwoody, L., Kernohan, W. G., & McCaughan, E. (2009). Development and evaluation of a problem-focused psychosocial intervention for patients with head and neck cancer. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *17*(4), 379–388. https://doi-org/10.1007/s00520-008-0480-7

Semple, C. J., Dunwoody, L., Kernohan, W.G., McCaughan, E., & Sullivan, K. (2008). Changes and challenges to patients' lifestyle patterns following treatment for head and neck cancer. *Journal of Advanced Nursing*, *63*(1), 85–93. https://doi-org/10.1111/j.1365-2648.2008.04698.x

Semple, C. J., Sullivan, K., Dunwoody, L., & Kernohan, W. G. (2004). Psychosocial interventions for patients with head and neck cancer: past, present, and future. *Cancer Nursing*, *27*(6), 434–441. https://doi-org/10.1097/00002820-200411000-00002

Sen, Y., Qian, Y., Koelmeyer, L., Borotkanics, R., Ricketts, R., Mackie, H., Lam, T. C., Shon, K. H., Suami, H., & Boyages, J. (2018). Breast Cancer-Related Lymphedema: Differentiating Fat from Fluid Using Magnetic Resonance Imaging Segmentation. *Lymphatic Research and Biology*, *16*(1), 20–27. https://doi.org/10.1089/lrb.2016.0047

Seward, C., Skolny, M., Brunelle, C., Asdourian, M., Salama, L., & Taghian, A. G. (2016). A comprehensive review of bioimpedance spectroscopy as a diagnostic tool for the detection and measurement of breast cancer-related lymphedema. *Journal of Surgical Oncology*, *114*(5), 537–542. https://doi.org/10.1002/jso.24365

Sharma, A., Méndez, E., Yueh, B., Lohavanichbutr, P., Houck, J., Doody, D.R., Futran, N.D., Upton, M.P., Schwartz, S.M., & Chen, C. (2012). Human papillomavirus-positive oral cavity and oropharyngeal cancer patients do not have better quality-of-life trajectories. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *146*(5), 739–745. https://doi.org/10.1177/0194599811434707

Shuy, R.W. (2003). In-person versus telephone interviewing. In Holstein JA & Gubrium JF (eds) *Inside interviewing: New Lenses, New Concerns.* Sage Publishing, Thousand Oaks CA. (pages 175-93)

Singer, S., Arraras, J., Chie, W.C., Fisher, S., Galalae, R., Hammerlid, E., Nicolatou-Galitis, O., Schmalz, C., Verdonck-de Leeuw, I.M., Gamper, E., Keszte, J., & Hofmeister, D. (2013) Performance of the EORTC questionnaire for the assessment of quality of life in head and neck cancer patients EORTC QLQ-H&N35. A methodological review. *Quality of Life Research* 22, 1927-1941. https://doi.org/10.1007/s11136-012-0325-1

Smith, J.A., Flowers, P., & Larkin, M. (2009). *Interpretive phenomenological analysis: theory, method, and research.* Sage Publishing, Thousand Oaks, CA.

Smith, A. W., & Jensen, R. E. (2019). Beyond methods to applied research: Realizing the vision of PROMIS®. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *38*(5), 347–350. https://doi.org/10.1037/hea0000752

Smith, B. G., Hutcheson, K. A., Little, L. G., Skoracki, R. J., Rosenthal, D. I., Lai, S. Y., & Lewin, J. S. (2015). Lymphedema outcomes in patients with head and neck cancer. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *152*(2), 284–291. https://doi.org/10.1177/0194599814558402

Smith, B. G., & Lewin, J. S. (2010). Lymphedema management in head and neck cancer. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *18*(3), 153–158. https://doi.org/10.1097/MOO.0b013e32833aac21

So, W. K., Chan, R. J., Chan, D. N., Hughes, B. G., Chair, S. Y., Choi, K. C., & Chan, C. W. (2012). Quality-of-life among head and neck cancer survivors at one year after treatment--a systematic review. *European Journal of Cancer (Oxford, England: 1990)*, *48*(15), 2391–2408. https://doi.org/10.1016/j.ejca.2012.04.005

Stamatakos, M., Stefanaki, C., & Kontzoglou, K. (2011). Lymphedema and breast cancer: a review of the literature. *Breast Cancer (Tokyo, Japan)*, *18*(3), 174–180. https://doi.org/10.1007/s12282-010-0246-1

Starmer, H.M., Abrams, R., Webster, K., Kizner, J., Beadle, B., Holsinger, F.C., Quon, H., Richmon, J. (2018). Feasibility of a mobile application to enhance swallowing therapy for patients undergoing radiation-based treatment for head and neck cancer. *Dysphagia,* 33(2), 227-33. https://doi.org/10.1007/s00455-017-9850-y

Starmer, H.M., Arrese, L., Langmore, S., Ma, Y., Murray, J., Patterson, J., Pisegna, J., Roe, J., Tabor-Gray, L., Hutcheson, K. (2021). Adaptation and validation of the Dynamic Imaging Grade of Swallowing Toxicity for Flexible Endoscopic Evaluation of Swallowing: DIGEST-FEES. *Journal of Speech, Language, and Hearing Research,* 64(6), 1802-10. https://doi.org/10.1044/2021_JSLHR-21-00014

Starmer, H. M., Cherry, M. G., Patterson, J., Fleming, J., & Young, B. (2023). Head and neck lymphedema and quality of life: the patient perspective. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *31*(12), 696. https://doi.org/10.1007/s00520-023-08150-2

Starmer, H., Cherry, M. G., Patterson, J., Young, B., & Fleming, J. (2023). Assessment of Measures of Head and Neck Lymphedema Following Head and Neck Cancer

Treatment: A Systematic Review. *Lymphatic Research and Biology*, *21*(1), 42–51. https://doi.org/10.1089/lrb.2021.0100

Starmer, H. M., Drinnan, M., Bhabra, M., Watson, L. J., & Patterson, J. (2021). Development and reliability of the revised Patterson Edema Scale. *Clinical Otolaryngology: Official Journal of ENT-UK; Official Journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*, *46*(4), 752–757. https://doi.org/10.1111/coa.13727

Starmer H.M., Finch K., & Dawson C. (2022). Experiences of caregivers providing therapy to people with head and neck lymphoedema after head and neck cancer. *Wounds International*. 13(1), 30-37.

Starmer, H. M., Hutcheson, K., & Patterson, J. (2023). Internal oedema and dysphagia characteristics in patients with head and neck cancer. *Clinical Otolaryngology: Official Journal of ENT-UK; Official Journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*, *48*(4), 700–704. https://doi.org/10.1111/coa.14046

Starmer, H.M., Klein, D., Montgomery, A., Goldsmith, T., McCarroll, L., Richmon, J., Holsinger F.C., Beadle, B., Jain, P. Head and Neck Virtual Coach: a randomized control trial of mobile health as an adjunct to swallowing therapy during head and neck radiation. *Dysphagia,* 38(3), 847-55*.* https://doi.org/10.1007/s00455-022-10506-5

Starmer, H.M., Yang, W., Gourin, C.G., Kumar, R., Jones, B., McNutt, T., Cheng, S., Quon, H. (2017). One-year swallowing outcomes in patients treated with prophylactic gabapentin during radiation-based treatment for oropharyngeal cancer. *Dysphagia,* 32(3), 437-42. https://doi.org/10.1007/s00455-017-9783-5

Starmer, H.M., Yang, W., Raval, R., Gourin, C.G., Richardson, M., Kumar, R., Jones, B., McNutt, T., Cheng, Z., Cheng, S., Quon, H. (2014). Effect of gabapentin on swallowing during and after chemoradiation for oropharyngeal squamous cell cancer. *Dysphagia,* 29(3), 396-402. https://doi.org/10.1007/s00455-014-9521-1

Stubblefield, M. D. (2011). Radiation fibrosis syndrome: neuromuscular and musculoskeletal complications in cancer survivors. *PM&R: the Journal of Injury, Function, and Rehabilitation*, *3*(11), 1041–1054. https://doi.org/10.1016/j.pmrj.2011.08.535

Suehiro, K., Morikage, N., Yamashita, O., Harada, T., Samura, M., Takeuchi, Y., Mizoguchi, T., Nakamura, K., & Hamano, K. (2016). Skin and Subcutaneous Tissue Ultrasonography Features in Breast Cancer-Related Lymphedema. *Annals of Vascular Diseases*, *9*(4), 312–316. https://doi.org/10.3400/avd.oa.16-00086

Sunderland, M., Matthews, C., Waterhouse, D., Shetty, S. & Morton, R.P. (2023). Unmet needs, quality of life and psychological distress: insights regarding head and neck cancer patients in a rural setting. The *Journal of Laryngology and Otology*. 137(1), 89-95. https://doi.org/10.1017/S0022215121001699

Tacani, P. M., Franceschini, J. P., Tacani, R. E., Machado, A. F., Montezello, D., Góes, J. C., & Marx, A. (2016). Retrospective study of the physical therapy modalities applied in head and neck lymphedema treatment. *Head & Neck*, *38*(2), 301–308. https://doi.org/10.1002/hed.23899

Taghian, N. R., Miller, C. L., Jammallo, L. S., O'Toole, J., & Skolny, M. N. (2014). Lymphedema following breast cancer treatment and impact on quality of life: a review. *Critical Reviews in Oncology/Hematology*, *92*(3), 227–234. https://doi.org/10.1016/j.critrevonc.2014.06.004

Thomson, O. (Host). (2021, July 4). The qualitative research series – More than methods? Thematic analysis with Dr Victoria Clarke. [Audio podcast episode 46]. In The Words Matter Podcast. https://www.droliverthomson.com/the-words-matter-podcast/

Toft, K., Best, C., & Donaldson, J. (2024). Assessment of patients with head and neck cancer using the MD Anderson Dysphagia Inventory: Results of a study into its comprehensiveness, comprehensibility and relevance to clinical practice. *International Journal of Language & Communication Disorders*, Advance online publication. https://doi.org/10.1111/1460-6984.13026

Torrance, G.W. (1987). Utility approach to measuring health-related quality of life. *Journal of Chronic Diseases*, 40(6), 593-600. https://doi.org/10.1016/0021-9681(87)90019-1

Tsubaki, M., Ito, Y., & Haniuda, Y. (2022). Further thoughts on how the electronic patient-reported outcome measure (ePROM) can be implemented in the real world. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer*, *31*(1), 58. https://doi.org/10.1007/s00520-022-07545-x

Turcotte, M. C., Herzberg, E. G., Balou, M., & Molfenter, S. M. (2018). Analysis of pharyngeal edema post-chemoradiation for head and neck cancer: Impact on swallow function. *Laryngoscope Investigative Otolaryngology*, *3*(5), 377–383. https://doi.org/10.1002/lio2.203

Uman, L. S. (2011). Systematic reviews and meta-analyses. *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie Canadienne de Psychiatrie de l'Enfant et de l'Adolescent*, *20*(1), 57–59.

Vallianou, N. G., Evangelopoulos, A., Kounatidis, D., Panagopoulos, F., Geladari, E., Karampela, I., Stratigou, T., & Dalamaga, M. (2023). Immunotherapy in Head and Neck Cancer: Where Do We Stand? *Current Oncology Reports*, *25*(8), 897–912. https://doi.org/10.1007/s11912-023-01425-1

Varpio, L., Ajjawi, R., Monrouxe, L.V., O'Brien, B.C., & Rees, C.E. (2017). Shedding the cobra effect: problematising thematic emergence, triangulation, saturation, and member checking. *Medical Education*, 51, 40-50. https://doi.org/10.1111/medu.13124

Varpio, L., & MacLeod, A. (2020). Philosophy of Science Series: Harnessing the Multidisciplinary Edge Effect by Exploring Paradigms, Ontologies, Epistemologies, Axiologies, and Methodologies. *Academic Medicine: Journal of the Association of American Medical Colleges*, *95*(5), 686–689. https://doi.org/10.1097/ACM.0000000000003142

Vasileiou, K., Barnett, J., Thorpe, S., & Young, T. (2018). Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. *BMC Medical Research Methodology*, *18*(1), 148. https://doi.org/10.1186/s12874-018-0594-7

Vodicka, E., Kim, K., Devine, E. B., Gnanasakthy, A., Scoggins, J. F., & Patrick, D. L. (2015). Inclusion of patient-reported outcome measures in registered clinical trials: Evidence from ClinicalTrials.gov (2007-2013). *Contemporary Clinical Trials*, *43*, 1–9. https://doi.org/10.1016/j.cct.2015.04.004

Wakefield, J. C. (2009). Disability and diagnosis: should role impairment be eliminated from DSM/ICD diagnostic criteria? *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *8*(2), 87–88. https://doi.org/10.1002/j.2051-5545.2009.tb00221.x

Weaver, K., & Olson, J. K. (2006). Understanding paradigms used for nursing research. *Journal of Advanced Nursing*, *53*(4), 459–469. https://doi.org/10.1111/j.1365-2648.2006.03740.x

Weiss, M.L., Domschikowski, J., Krug, D., Sonnhoff, M., Nitsche, M., Hoffmann, W., Becker-Schiebe, M., Bock, F., Hoffmann, M., Schmalz, C., Dunst, J., & Fabian, A. (2023). The impact of palliative radiotherapy on health-related quality of life in patients with head and neck cancer - Results of a multicenter prospective cohort study. *Clinical and Translational Radiation Oncology*. 41:100633. Published 2023 Apr 26. https://doi.org/10.1016/j.ctro.2023.100633

Weldring, T., & Smith, S. M. (2013). Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health Services Insights*, *6*, 61–68. https://doi.org/10.4137/HSI.S11093

Welsh Index of Multiple Deprivation, 2020. https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation. Accessed September 16, 2022.

Weymuller, E. A., Jr, Alsarraf, R., Yueh, B., Deleyiannis, F. W., & Coltrera, M. D. (2001). Analysis of the performance characteristics of the University of Washington Quality of Life instrument and its modification (UW-QOL-R). *Archives of Otolaryngology--Head & Neck Surgery*, *127*(5), 489–493. https://doi.org/10.1001/archotol.127.5.489

Weymuller, E. A., Yueh, B., Deleyiannis, F. W., Kuntz, A. L., Alsarraf, R., & Coltrera, M. D. (2000). Quality of life in patients with head and neck cancer: lessons learned from 549 prospectively evaluated patients. *Archives of Otolaryngology--Head & Neck Surgery*, *126*(3), 329–336. https://doi.org/10.1001/archotol.126.3.329

Whiting, P. F., Rutjes, A. W., Westwood, M. E., Mallett, S., Deeks, J. J., Reitsma, J. B., Leeflang, M. M., Sterne, J. A., Bossuyt, P. M., & QUADAS-2 Group (2011). QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine*, *155*(8), 529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

Wiering, B., de Boer, D., & Delnoij, D. (2017). Patient involvement in the development of patient-reported outcome measures: a scoping review. *Health Expectations: An International Journal of Public Participation in Health Care and Health Policy*, *20*(1), 11–23. https://doi.org/10.1111/hex.12442

Wiering, B., de Boer, D., & Delnoij, D. (2017). Patient involvement in the development of patient-reported outcome measures: The developers' perspective. *BMC Health Services Research*, *17*(1), 635. https://doi.org/10.1186/s12913-017-2582-8

Williamson, P. R., Altman, D. G., Bagley, H., Barnes, K. L., Blazeby, J. M., Brookes, S. T., Clarke, M., Gargon, E., Gorst, S., Harman, N., Kirkham, J. J., McNair, A., Prinsen, C. A. C., Schmitt, J., Terwee, C. B., & Young, B. (2017). The COMET Handbook: version 1.0. *Trials*, *18*(Suppl 3), 280. https://doi.org/10.1186/s13063-017-1978-4

Wilkie, J. R., Mierzwa, M. L., Yao, J., Eisbruch, A., Feng, M., Weyburne, G., Chen, X., Holevinski, L., & Mayo, C. S. (2019). Big data analysis of associations between patient reported outcomes, observer reported toxicities, and overall quality of life in head and neck cancer patients treated with radiation therapy. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*, *137*, 167–174. https://doi.org/10.1016/j.radonc.2019.04.030

Williamson, P. R., Altman, D. G., Bagley, H., Barnes, K. L., Blazeby, J. M., Brookes, S. T., Clarke, M., Gargon, E., Gorst, S., Harman, N., Kirkham, J. J., McNair, A., Prinsen, C. A. C., Schmitt, J., Terwee, C. B., & Young, B. (2017). The COMET Handbook: version 1.0. *Trials*, *18*(Suppl 3), 280. https://doi.org/10.1186/s13063-017-1978-4

Wilson, I. B., & Cleary, P. D. (1995). Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *Journal of the American Medical Association*, *273*(1), 59–65. https://doi.org/10.1001/jama.1995.035202250075037

Wilson, K. A., Dowling, A. J., Abdolell, M., & Tannock, I. F. (2000). Perception of quality of life by patients, partners and treating physicians. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *9*(9), 1041–1052. https://doi.org/10.1023/a:1016647407161

Wong Riff, K. W., Tsangaris, E., Goodacre, T., Forrest, C. R., Pusic, A. L., Cano, S. J., & Klassen, A. F. (2017). International multiphase mixed methods study protocol to develop a cross-cultural patient-reported outcome instrument for children and young adults with cleft lip and/or palate (CLEFT-Q). *BMJ Open*, *7*(1), e015467. https://doi.org/10.1136/bmjopen-2016-015467

Wood-Dauphinee, S., & Williams, J. I. (1987). Reintegration to Normal Living as a proxy to quality of life. *Journal of Chronic Diseases*, *40*(6), 491–502. https://doi.org/10.1016/0021-9681(87)90005-1

World Health Organization. *International Classification of Impairments, Disabilities, and Handicaps: A manual of classification relating to the consequences of disease*. Geneva 1980.

World Health Organization. *Towards a Common Language for Functioning, Disability, and Health: ICF, The International Classification of Functioning, Disability, and Health*. Geneva 2002.

Xu, B., Boero, I. J., Hwang, L., Le, Q. T., Moiseenko, V., Sanghvi, P. R., Cohen, E. E., Mell, L. K., & Murphy, J. D. (2015). Aspiration pneumonia after concurrent chemoradiotherapy for head and neck cancer. *Cancer*, *121*(8), 1303–1311. https://doi.org/10.1002/cncr.29207

Yang, W., McNutt, T.R., Dudley, S.A., Kumar, R., Starmer, H.M., Gourin, C.G., Moore, J.A., Evans, K., Allen, M., Agrawal, N., Richmon, J.D., Chung, C.H., Quon, H. (2016). Predictive factors for prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement and use in head and neck patients following Intensity Modulated Radiation Therapy (IMRT) treatment: concordance, discrepancies, and the role of gabapentin. *Dysphagia,* 31(2), 206-13. https://doi.org/10.1007/s00455-015-9679-1

Yao, T., Beadle, B., Holsinger, F.C., Starmer, H.M. (2020). Effectiveness of a home-based head and neck lymphedema management program: a pilot study. *Laryngoscope,* 130(12), E858-62. https://doi.org/10.1002/lary.28549

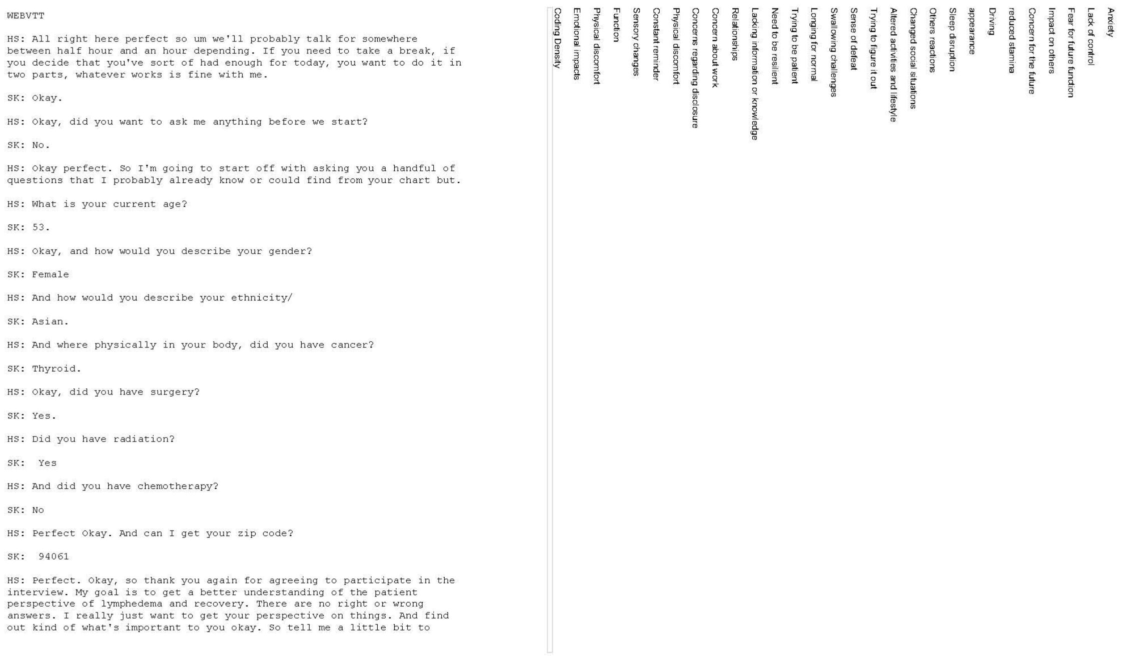
Yardley, L. (2008). Demonstrating validity in qualitative psychology. In JA Smith (ed.) *Qualitative Psychology: A practical guide to research methods., 2nd Edition*. (pp 235-51). Sage Publishing, London.

Yin, R.K. (2015). *Qualitative research from start to finish*. Guilford publications, London.

Zhu, G., Amin, N., Herberg, M. E., Maroun, C. A., Wang, H., Guller, M., Gourin, C. G., Rooper, L. M., Vosler, P. S., Tan, M., D'Souza, G., Koch, W. M., Eisele, D. W., Seiwert, T. Y., Fakhry, C., Pardoll, D. M., & Mandal, R. (2022). Association of Tumor Site with the Prognosis and Immunogenomic Landscape of Human Papillomavirus-Related Head and Neck and Cervical Cancers. *JAMA Otolaryngology-- Head & Neck Surgery*, *148*(1), 70–79. https://doi.org/10.1001/jamaoto.2021.3228

Appendices

Appendix 1: Sample transcription and coding in NVivo



WEBVTT

HS: All right here perfect so um we'll probably talk for somewhere between half hour and an hour depending. If you need to take a break, if you decide that you've sort of had enough for today, you want to do it in two parts, whatever works is fine with me.

SK: Okay.

HS: Okay, did you want to ask me anything before we start?

SK: No.

HS: Okay perfect. So I'm going to start off with asking you a handful of questions that I probably already know or could find from your chart but.

HS: What is your current age?

SK: 53.

HS: Okay, and how would you describe your gender?

SK: Female

HS: And how would you describe your ethnicity/

SK: Asian.

HS: And where physically in your body, did you have cancer?

SK: Thyroid.

HS: Okay, did you have surgery?

SK: Yes.

HS: Did you have radiation?

SK: Yes

HS: And did you have chemotherapy?

SK: No

HS: Perfect Okay. And can I get your zip code?

SK: 94061

HS: Perfect. Okay, so thank you again for agreeing to participate in the interview. My goal is to get a better understanding of the patient perspective of lymphedema and recovery. There are no right or wrong answers. I really just want to get your perspective on things. And find out kind of what's important to you okay. So tell me a little bit to

SK: And it's the same with my family. They're amazing they do, so much so.

HS: Nice. Have you run into situations where people maybe that you don't know as well, or people are asking you about that? tell me a little bit about that experience for you.

SK: That's, that's the kind of visible the physical characteristics of this whole thing.

HS: Yeah.

SK: Um. You know a lot of the times when I'm around people that I don't know or whatever I have a sco- scarf on. And so, then you know, especially in the summer, people are just like, "So tell me why you have a scarf on" or you know people that I haven't met in a while will comment on the voice. And say you know, "You don't quite sound right", you know "what's going on?" And then, when they do see there's it's really visible.

HS: Mhm.

SK: I mean. Again, I know how far I've come. And I'm so grateful for how it looks now. But for people that are not aware…

HS: Sure

SK: It's still pretty visible.

HS: Sure, sure, and how does that impact you when people ask those questions or?

SK: It's hard, I mean it's, it's not something I shy away from talking about because I just feel like the more I share my experience, the more information gets out there and i'm okay. It's just tiring at times. It's like okay i'm tired of telling one more person I had cancer so…

HS: Right, yeah.

SK: And then it's also the, I mean, there are people that, I mean fair, I mean it's fair they they react, the way they take that information in. And it depends right? I mean older people will automatically, many of them, especially in my culture they'll automatically equate cancer with death. So that's right away, it's like "oh my God," you know, "are you dying" and "no not yet. I'm not dying yet." So it's, it's kind of dealing with how they take in the information that gets tiring.

HS: Sure sure tell me a little bit more about that that sort of cultural difference of, of perception of cancer and lymphedema, how do you how do you think that plays a role for you?

SK: I think it's… so that's perhaps when this whole family base comes out right? I mean my mom lives with me. um and it's kind of an out of body experience you're going through what you're going through, but you're

HS: Okay, what are some of those.

SK: Um…Breads, rice, any any kind of cracker, cookies, chips none of those things, I mean. It's forcing me towards a healthier diet. And I'd like to consciously make that choice and not have it made for me.

HS: Not be forced, yeah. That makes sense.

SK: I'm not much of a junk food eater but now that it just won't go down, I won't stop trying.

HS: Right

SK: To see if it's improved.

HS: Right.

SK: And it hasn't.

HS: Right okay. How has the lymphedema impacted your work and your daily routine?

SK: Again I think in terms of confidence I've come a long way. I still tend to kind of shy away. Um if I don't have to meet someone that I try not to. But because it impacts speech a lot it's like you know the dry mouth. I can sustain a conversation for a few minutes, and then I have to drink water. So I think I haven't felt the full brunt of it. Yet, because school starts in the fall and that's when I'm going to have to really give my presentations and stuff and then my college classes start. And then lecturing is a whole other challenge that I'm, I'm not sure how i'm going to navigate that at all.

HS: Okay. Okay, do you feel like the lymphedema itself impacts, your speech or your voice?

SK: So I don't know how much of that is related. Whether lymphedema and the dry mouth are linked in some way or not. Or as one improves is the other automatically going to improve? I'm not entirely sure of that.

HS: How about um, your family? has there been an impact on your family with the lymphedema?

SK: No.

HS: No okay how about other relationships? other people?

SK: No. um for the most part, my my my immediate colleagues, I mean I I stayed in touch with them throughout this whole journey. They are really well aware of everything that I've been through. And I'm very lucky that they're as supportive as they are. So I don't get too many questions from them, even if they noticed something. They just kind of go "umph" You know "I'm sure she'll work through it"

HS: Sure.

also watching the domino impact on everybody around you. And my mom who just recently immigrated from India came to live with me. She's been here two years now. But she's one right? I mean when I got my diagnosis, I didn't know… forget… I didn't know whether I was going to pull through it. I didn't know how she was going to pull through it. It's just… because the you know… we're, we're all in a world where you know we have access to information, and we trust our doctors and you know we have a health system that supports our well-being. She doesn't come from that culture.

HS: Okay.

SK: So India, the health care system, I mean there's, there's very good health care out there, but how they treat patients is very different from how people are treated here.

HS: Okay.

SK: So kind of seeing how she dealt with it or kind of you know… not being able to understand why I would want to tell anybody that I have cancer…

HS: Mhm.

SK: Or lymphedema you know? She's like "oh just tell them you have a sinus infection." you know "and your glands are swollen you don't, why do you need to tell them you have cancer?" so… There was a lot of that that I kind of had to work through with her in being, and also being sensitive to where she was coming from.

HS: Sure, sure. That sounds like a challenging, a challenging added dilemma there yeah.

SK: Yeah.

HS: How did you work through that?

SK: I think just lots of talking through and some of it was like, "I just have to tell people. I cannot just tell them I'm going on disability and not tell them why." I, you know so there was a lot of that, but I think you know again it's like every other Indian family that, "don't tell them." And I was like I, I cannot, I cannot keep up this tell this one, but don't tell that one you know? And I know that she was coming at it from a protective stance of.

HS: Sure.

SK: I just don't want people to, to assume that you're not going to make it through this you know?

HS: Right, right.

SK: And I was like "no I, I'll be fine and you know people are going to have to get over whatever it is that they're thinking."

Coding Density
Emotional impacts
Physical discomfort
Function
Sensory changes
Constant reminder
Physical discomfort
Concerns regarding disclosure
Concern about work
Relationships
Lacking information or knowledge
Need to be resilient
Trying to be patient
Longing for normal
Swallowing challenges
Sense of defeat
Trying to figure it out
Altered activities and lifestyle
Changed social situations
Others reactions
Sleep disruption
appearance
Driving
reduced stamina
Concern for the future
Impact on others
Fear for future function
Lack of control
Anxiety

there's still hope for it to get better, but I guess the question remains is you know, is this going to be chronic? To some extent I'm going to have to deal with kind of the tightness in my neck area.

HS: yeah

SK: For a while.

HS: How does it feel now that it's better? you described it as being very sort of tight in the past. How does it feel now?

SK: I think it's the same like when, when it gets when it impacts significantly uh… it's, it's I mean it's tight, really tight and it's mostly along the sides of my neck.

HS: Okay.

SK: That I feel it the worst.

HS okay. And how is that what kinds of problems is this like to for you?

SK: Say that again.

HS: What kinds of problems has the swelling caused for you?

SK: Oh, I think I think, from a psychological point of view it's, it's just a constant reminder. that not all is quite right.

HS: yeah.

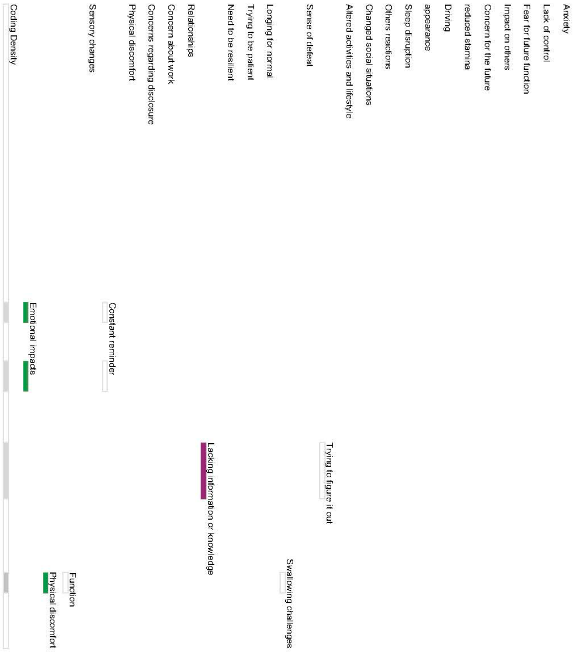
SK: It is it just never goes away so it's like something that all day long I'm reminded that there's something significant that I'm dealing with.

HS: sure.

SK: Too I'm not sure how much it's related to the dry mouth and the swallowing issues that I'm having. So there's that. And then I guess I'm still in the processing phase of trying to find out what foods kind of make it worse, or you know. If I eat later in the night are the symptoms better in the morning, you know, so I i'm still very much playing the game right now.

HS: Sure sure. Tell me about how, when you were more swollen did the swallowing see mark challenging to you and and, if so, how was it different than you think it is now that the swelling's a little bit less?

SK: Oh, I think I think things have gotten way better when the swelling was really when the swelling was bad, pretty much I was on liquids like there was nothing that was going down other than liquids. And even that like even soups and stuff had to be strained and diluted and, and now I think I've come a long way towards a normal, more normal diet with certain textures that are an absolute no go.



SK: um. One, of course, again the visible part of it. And just being super self-conscious. So that's one aspect of it that I'm dealing with. And then physically it's you know not being able to bend your chin down. It's the, you know, the stretching on the sides. Driving becomes a handicap because um you know, so there are times when I have to sit like at the end of the day, I have to sit in the parking lot and make sure I stretch, before I begin.

HS: Yeah sure.

SK: It's gotten super stiff.

HS: yeah

SK: um by 830 900 it's stretched tight. So, it's forcing me now to go to bed early simply because i'm tired of dealing with that.

HS: Mhm, sure. Is that then limit other other activities that you would like to be doing?

SK: Absolutely. Right it's, it's… you know, hinders being able to go out. You know? I mean, again, like I think a large part of it, it's also a dry mouth and not being able to eat effectively. And then on top of that feeling this constant pain.

HS: Sure, sure. How about good day? How does a good day look different than a bad day?

SK: I think um, minimal kind of that feeling of being stretched thin. More stretches of time when I'm not as aware of it.

HS: Mhm.

SK: At all times. I think, then I come away and go "oh wait I haven't been like just massaging my neck all day long." You know? Or I don't remember doing it so those I feel like are "oh wow you know. I've had a good day." But there's a lot, you know I feel like so much of my movements have changed. I find my hands kind of autopiloting to my neck and my face all the time. So having to stretch my skin out quite a bit. Um… I'm also an information junkie so I'm like constantly trying to see if I can find articles or solutions to this that.

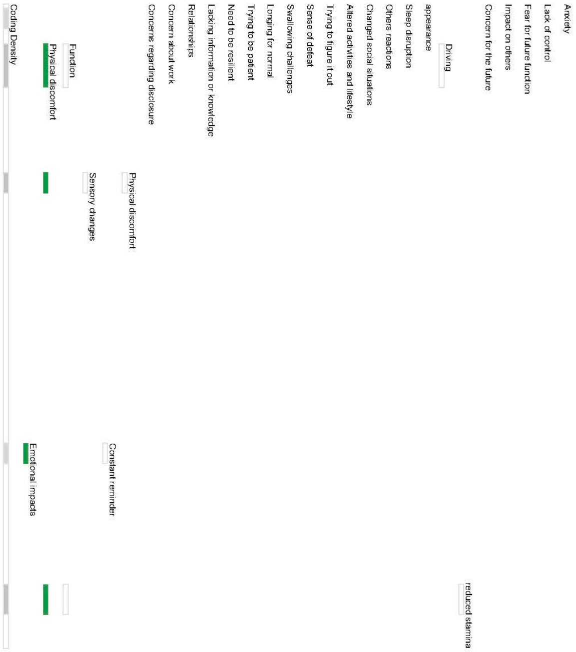
HS: Sure.

SK: that'll give me relief, but yeah.

HS: What kinds of activities do you do you want to be doing that you can't do because of the lymphedema or that you're limited in?

SK: I don't, I don't think I'm really limited myself. I think it's, I'm able to go out and do what I want to do, it's just the length of time that I'm able to sustain it.

HS: Okay.



SK: That, that gets impacted. I mean, I mean again, like driving. I mean I'm driving. But do I now feel confident about just saying, "I can take an hour long drive and be just fine."

HS: Mhm. Okay. Are there other things like that that you've noticed as well that that tend to be impacted more than other things?

SK: Um. No, I mean again, I haven't been out and about so much, but you know I, I was in a good pattern before then hysterectomy. As in a good pattern of exercise. I was on the elliptical almost 40 to 45 minutes a day.

HS: Sure.

SK: And that didn't this didn't seem to impact. If anything, it helped. So, and that's something I want to get back into.

HS: Yeah as you recover. Sure. Um if, if I had like a magic wand and I could make the lymphedema go away completely, how would life look different to you?

SK: Oh, my gosh just no pain. No pain. It's the one thing that reminds me all day long. It just feels like oh… like there's just I'm just carrying the head now. Instead of it just being naturally.. it just feels like very much separated.

HS: mm hmm. yeah.

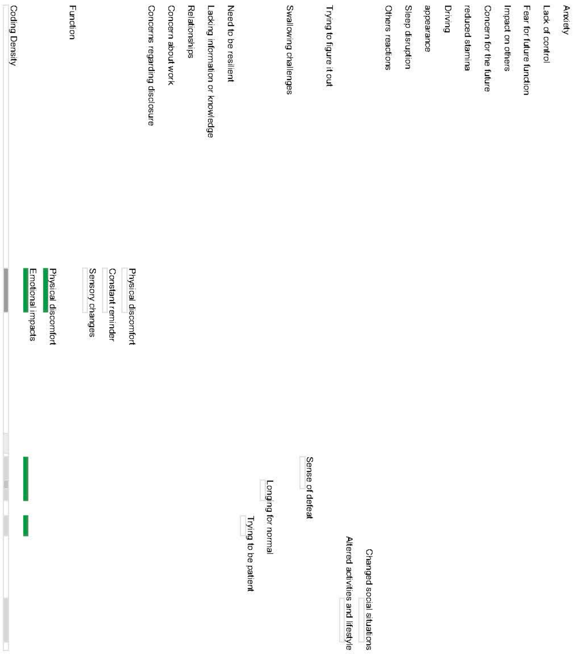
SK: Just not pain.

HS: yeah. Noww, you know our experiences with health are not always physical and you've sort of talked a little bit about how its impacted you in other ways, but how do you think the lymphedema impacts you from a mood or an emotional perspective?

SK: I think emotionally, I think that's, that's what it is. It's, it's kind of constantly battling the image, image of the self that you have. And you know looking in the mirror and contending with it. I mean, no matter how much you know it, you look in the mirror and you you're like, "okay. It's still there." Like you, wake up in the morning and you're like, "okay it's, today it's going to be better." And no, it's not. So it's, it's the time that it's taking. It's, it's having the patience to wait it out. Or the patience to kind of go, "alright, it's bad today, but that doesn't mean it's going to be bad tomorrow." You know? And the days when it's really bad it just, I'm done. I just, I just go to bed.

HS: Yeah.

SK: So it's hard. I mean that and I know... I mean my family will not say anything to me at all. But you know, certainly impacts mood. It's impacts how much I'm willing to sit there and have a conversation that's not around this and not be self-absorbed and whiny. So, I, I give up there are days when I just say "okay I'm calling it a day."



HS: Mhm.

SK: I mean family back home in India, does not know yet.

HS: Okay.

SK: I mean it wasn't something I went out and publicly announced to the world.

HS: Sure.

SK: But you know I have very close cousins and aunts and uncles and back home in India who have no clue.

HS: Sure

SK: That I went through any of this last year.

HS: Mhm. Have you had any difficulties with breathing relating to the lymphedema?

SK: No.

HS: Okay how about sleeping?

SK: Yes, um a lot of stiffness in the neck area so it's like turning is hard.

HS: Okay.

SK: Stretching is hard. Turning left to right, it's just I immediately feel the stretch on the neck. And when I wake up in the morning it's pretty significant. I mean, it's down now but couple of months back the massage and the mask was a go to first thing in the morning.

HS: Got it. And does it interfere with your ability to sleep at night?

SK: Yes, and . Some, I mean there are times when I have to sit up and kind of just massage it through.

HS: Okay.

SK: To kind of relieve the pain. I'm not doing it as much now, but there were nights that I would just take an advil. Because I couldn't do it anymore.

HS: Sure.

SK: And I just wanted to sleep.

HS: Yeah, yeah. Can you sort of take me through a bad day with the lymphedema what does that look like, for you?

SK: I mean, she did say there’s support. And you know this is right about the time that people end up needing that because the anxiety sets in.

HS: Right.

SK: And it is something I'm, I'm, I'm kind of trying to be aware of for myself. Like is this something that I'm dwelling on a lot? The anxiety is definitely there. The fear is definitely there.

HS: Yeah yeah. Yeah, I think that the transition from sort of active treatment to more long term, it's, it's challenging for a lot of people.

SK: Yeah and it feels scary I mean. You know? Dr Beadle that way has been amazing. She's, even yesterday, she was like “oh doesn't look like you know you know Dr Chan or Dr Orloff are seeing you until the end of the year. So that I think I'll just see you in October.” And it's just, it's just a relief. You know, she's like “I see you have a check in with heather and then after that you'll see me. It's good for you to see one of us every few months, so you, you don't feel like you're just kind of out there.”

HS: Sure. That connection to the team and… yeah. When you think back to when we first met and started doing the lymphedema therapy, how did you feel about the therapy early on?

SK: I mean, I think, I think very hopeful. Because again, like I said, we can.. you know yo,u you right away the minute you hear what treatment you're going to go through you, you, you open your laptop and there's plenty of information out there.

HS: sure.

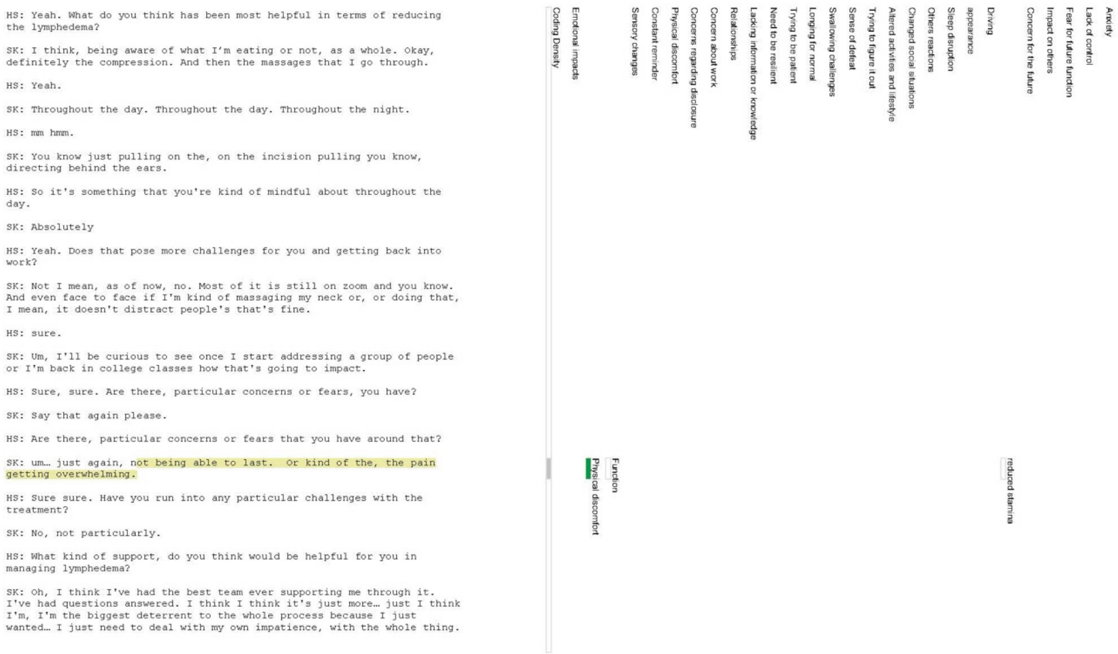
SK: Not all of it right. But you get on patient forums and stuff. And you hear about Oh, you know, “compression therapy really helps” and you know “it's really effective.” And so I think, I think very hopeful. And I did, I think I, I have seen a very positive turnaround. From when I started the compression so…I’m very encouraged by the whole thing. But then, as things start improving you also start getting impatient and….

HS: sure.

SK: You see, you just want it all done now, like you know, “Why can't it just be gone?”

HS: Right, the there's, those feelings change with time as, as you move from acute or chronic, yeah.

SK: I mean it's just, it's hard right. I mean, I mentioned the visible signs. The surgery scar seems to be fading. All the radiation kind of pigmentation stuff is also seems to be resolving for the most part. But then there's the lymphedema. The one last thing like, “just go down.” So I don't have to explain that. I don't have to worry about it.



HS: Yeah. What do you think has been most helpful in terms of reducing the lymphedema?

SK: I think, being aware of what I’m eating or not, as a whole. Okay, definitely the compression. And then the massages that I go through.

HS: Yeah.

SK: Throughout the day. Throughout the day. Throughout the night.

HS: mm hmm.

SK: You know just pulling on the, on the incision pulling you know, directing behind the ears.

HS: So it's something that you're kind of mindful about throughout the day.

SK: Absolutely

HS: Yeah. Does that pose more challenges for you and getting back into work?

SK: Not I mean, as of now, no. Most of it is still on zoom and you know. And even face to face if I'm kind of massaging my neck or, or doing that, I mean, it doesn't distract people's that's fine.

HS: sure.

SK: Um, I'll be curious to see once I start addressing a group of people or I'm back in college classes how that's going to impact.

HS: Sure, sure. Are there, particular concerns or fears, you have?

SK: Say that again please.

HS: Are there, particular concerns or fears that you have around that?

SK: um… just again, not being able to last. Or kind of the, the pain getting overwhelming.

HS: Sure sure. Have you run into any particular challenges with the treatment?

SK: No, not particularly.

HS: What kind of support, do you think would be helpful for you in managing lymphedema?

SK: Oh, I think I've had the best team ever supporting me through it. I've had questions answered. I think I think it's just more… just I think I'm, I'm the biggest deterrent to the whole process because I just wanted… I just need to deal with my own impatience, with the whole thing.

HS: mm hmm. That sounds exhausting.

SK: It is.

HS: Tell me a little…

SK: I mean, I come to work. It helps to be here and to feel productive and to not, you know… I have to put this aside. I have to focus on that so that helps.

HS: Sure. Distraction. Tell me about your first experiences and starting treatment for the lymphedema.

SK: I think. I mean, I think I was hopeful uh…when I first started the treatment because it was fairly soon after the radiation and I just said, " ah…you know all this is part of everything that I've been through." I think I'm getting to a point where I'm more resigned now.

HS: Okay.

SK: Like just feeling like "all right, well, perhaps this is about as good as it gets." And, you know, I'm expecting miracles when there aren't any.

HS: Mhm.

SK: or…

HS: How does that make you feel?

SK: I have to put it out of my head Heather. I, I, I try not to dwell on it, but like I said, there are days, where it's so significant and so tight.

HS: yeah.

SK: It gets defeating.

HS: Sure.

SK: And then, you know, you also wonder… and this is something I mentioned to Dr Beadle too, every little thing, you wonder if this thing is coming back? is this is this a sign, you know?

HS: Sure.

SK: Oh, the swelling is really bad today. You know, does this mean something is wrong? I mean it's like… The mind wanders.

HS: Yeah Yeah. It's a very common thing I think a lot of people struggle with.

HS: Go easy on yourself.

SK: I try. Oh there are just mornings, when you wake up and you know you’re just like, “I don't want to see that.” You know? I just want to look normal and feel well. And you know you don’t. You don't you don't look normal. And you don't feel well. Um

HS: Yeah.

SK: You know that's, that's a mental battle that you, you, you work through the whole day.

HS: Mhm, yeah. Do you have concerns about the future with the lymphedema?

SK: I mean. I guess just questions around it. It's more, you know, is you know what, what harm is it doing with the lymph nodes blocked like that? You know, is it that, you know could that lead to other issues that you know?

HS: Sure.

SK: I have, I have questions, I think that are kind of coming to my mind, now.

HS: sure.

SK: I didn't have the bandwidth to even think it through.

HS: yeah.

SK: Now I'm starting to wonder, you know what is pooling like that, what is that doing? Doing when it's already sensitive.

HS: Right.

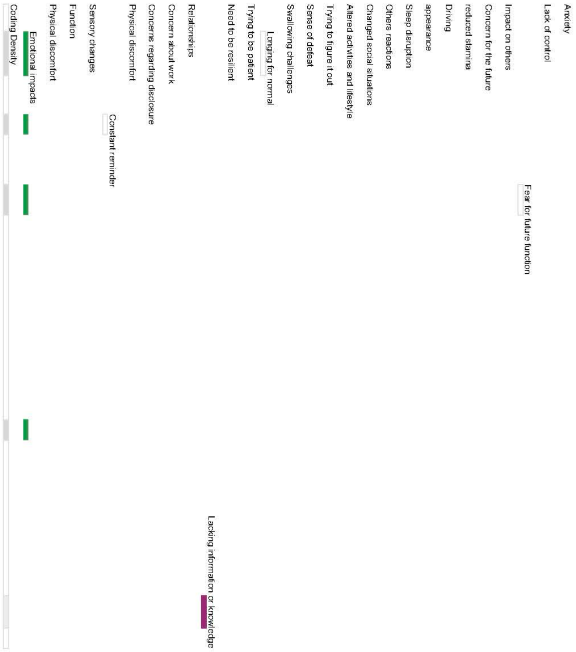
SK: You know, and again in my mind I'm always like, “am I doing everything that that is like you know, to treat this?”

HS: right.

SK: Or are there other things that I should be looking…

HS: Mhm. Yeah it's a big one of the questions that that we have is you know around information and what information would be helpful for you and and when is the appropriate time to provide that information I don't know if you have any thoughts about that.

SK: No, I mean, I think I think for me…if I think back now, I would say Oh, you know, maybe as the whole radiation treatment was going on, if that this was one of the things that was kind of mentioned to me, as you know, “hey, this is something you. you're going to have to work through after radiation.” But then I then I also think back and go “did I have the bandwidth to even process that?” I probably didn’t.



HS: hmm.

SK: So I, I honestly don't quite know I think, I think, I think, in reality, you know it happened. It became more of a significant issue for me and then I am having to work through it. I don't think there's a particular timeline really in terms of when this information needed to be brought forward. I think it's just more….yeah. I mean it's just, is there anything else out there that can be done for this? that's, that's…

HS: So you're sort of in an information seeking phase now?

SK: Yes, very much. And information that's more targeted towards something that's actionable. Oh great with the dry mouth let's go try the acupuncture. Great, I'm on it. I'm actually, I have an appointment for this Friday so.

HS: Great.

SK: I'm on it. I'm, I'm trying it and I feel fortunate that you know I'm working with the team that I'm working with, the medical team. And then you know the insurance and the access that I have to, to medical help.

HS: yeah.

SK: I know not everybody's this fortunate. So I'm very grateful and appreciative for that. And then I just feel like "alright, now that I have access to all of that, am I tapping every resource that?"

HS: Sure, sure absolutely. If you were to try to sort of break the three main ways that the lymphedema has impacted, you what sort of stands out?

SK: I think physical appearance. The emotional bandwidth and the resilience to, to power through that.

HS: yeah.

SK: And then though, the kind of physical pain. Of feeling like there's, there's a whole different something that doesn't quite belong that's over here, all day long.

HS: Sure, yeah. Describe what that pain feels like to you.

SK: Like just every fiber in my neck is just stretched tight. And I, it's, it's weird because there are days when I can touch the area and it's completely taut. And there are days when I feel like that inside. But then there is some movement of the skin area on the outside.

HS: okay.

SK: Days when I cannot move my skin at all. Like paper stretched.

HS: yeah.

SK: But like right now I can, I'm feeling the tightness inside. And I'm still able to shift and move.

HS: Okay.

SK: The skin on the outside. Just lots of things that I'm discovering about that whole area.

HS: Sure, sure. awareness in areas that we don't usually pay attention to.

SK: Yes. And not something that you take for granted it's just…

HS: Right right.

SK: It's hard. I mean, it's just, I mean now, now kind of the sensation has returned quite a bit. But there are days when I , I if I just get scared. I mean I'll see a drop of water kind of trickling down and I won't feel it at all.

SK: And it's unnerving.

HS: sure.

SK: Because you can see it and you just don't feel it.

SK: You know, that's weird.

HS: yeah. Hard to adjust to so many things at once.

SK: It's, it's so much of it is just the mental battle of it.

HS: mm hmm. yeah.

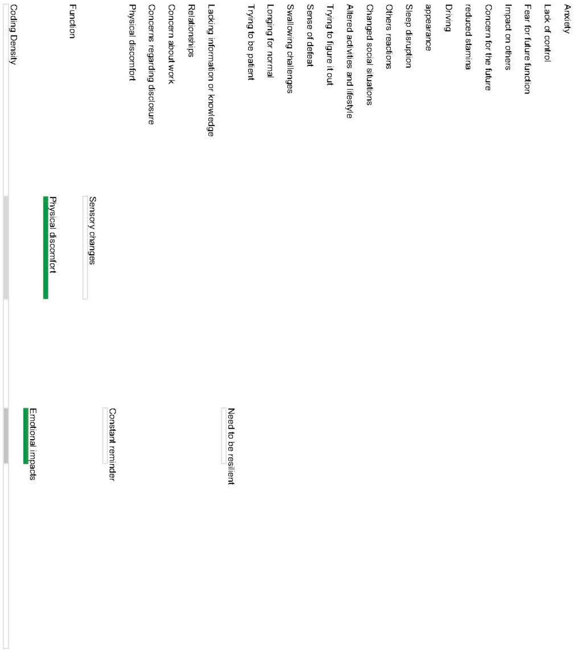
SK: I mean people talk about "stay positive." And you know, you know powering through it and it's hard when there's something that's a very visible physical reminder every second of the day. It's very hard to continually stay positive. And that in and of itself exhausts you by the end of the day.

HS: Absolutely, absolutely understand that. This has certainly been really, really helpful for me. Um are there, are there other things that you would like to share with me or that you think I need to know about?

SK: Not, not specific. Heather I mean, thanks to you for being part of this journey from the beginning. I mean, I'm I just feel so comfortable and it, it is like I said it's, it's, it's a source of strength, I mean I, I have my family. I have my friends who've been an immense support. But having a medical team that you trust and...

HS: Mhm

Sk: You kind of know you can go to.



Appendix 2: Initial item list for PROM

Emotional impacts

- I am frustrated by my lymphoedema.
- I feel sad when I think about my lymphoedema.
- When my lymphoedema makes it hard to socialize, I feel depressed.
- When my lymphoedema makes it hard to swallow, I feel depressed.
- I worry about how my lymphoedema will impact my ability to enjoy meals with others.
- My lymphoedema makes me feel like I am not a normal person.
- My physical appearance because of the lymphoedema upsets me.
- I feel isolated from my loved ones because of my lymphoedema.
- I wish that people around me understood my lymphoedema better.
- Because of my lymphoedema I feel I will never be normal again.
- I felt surprised when I developed lymphoedema.
- I get angry about my lymphoedema.
- I get frustrated when I do everything I need to do and the lymphoedema does not improve.
- I get tired of explaining my lymphoedema to people.
- I want to hide my lymphoedema behind a mask.
- I think about my lymphoedema constantly throughout the day.
- I’m embarrassed by my lymphoedema.
- I feel like people are staring at me because of my lymphoedema.
- I worry about the lymphoedema getting worse in the future.
- I feel uncomfortable when people notice my lymphoedema.
- I don’t want to have to talk to others about my lymphoedema.
- I worry when my voice changes because of my lymphoedema.
- I worry about my breathing when my lymphoedema is bad.
- I feel defeated when my lymphoedema is bad.
- I worry that I will get skin infections because of my lymphoedema.
- My lymphoedema is a constant reminder that something is wrong.
- I am tired of having to deal with lymphoedema.
- I feel ridiculous using my lymphoedema compression garments.
- It bothers me how visible my lymphoedema is.
- I worry about how the lymphoedema will impact me as I get older.
- I am bothered by how I look because of the lymphoedema.
- I am grateful when people do not notice my lymphoedema.
- I worry about the impact my lymphoedema has on my job.
- I am hopeful that things will get better with my lymphoedema.
- My lymphoedema is a constant reminder that all is not right.
- I lack self-confidence because of my lymphoedema.
- I battle with my self-image because of my lymphoedema.

- I feel impatient with my lymphoedema recovery.
- My lymphoedema impacts my mood.
- My lymphoedema makes me worry that my cancer is coming back.
- When I am more swollen, I worry that something else is wrong with my body.
- My lymphoedema makes me anxious.
- Sometimes I think to myself “why can’t the lymphoedema just be gone?”
- I get impatient about the pace of my recovery.
- I am worried that lymphoedema may cause other health issues.
- I need to be resilient in dealing with my lymphoedema.
- It is hard to stay positive because of my lymphoedema.
- I am hopeful that my lymphoedema will improve over time.
- I am unhappy because of my lymphoedema.
- I worry that if I don’t manage the lymphedema now, I will be stuck with it forever.
- The uncertainty about my lymphoedema in the future is difficult for me.
- When my swelling increases, I worry that my cancer has come back.
- I have difficulty accepting my lymphoedema.
- I will never get used to having lymphoedema.
- I have accepted that this is the new me.
- I am not concerned with my lymphoedema.
- My new appearance depresses me.
- I feel like I have no control over my lymphoedema.
- I get angry when I am swollen.
- I hate my lymphoedema.
- I dwell on my lymphoedema frequently.
- Having lymphoedema makes me feel anxious.
- My self-image is impacted by my lymphoedema.
- Being bothered by my lymphoedema makes me feel vane.
- I have lost a piece of myself due to lymphoedema.
- I worry that people are staring at my lymphoedema.
- I am self-conscious about my lymphoedema.
- I worry about how my co-workers and clients view me because of my lymphoedema.
- I am bothered by needing to tell people about lymphoedema.
- I feel desperate to get rid of the lymphoedema.
- I am frustrated that I don’t have the tools to make the swelling go away.
- I feel empowered to make my lymphoedema better.
- It feels good to have something I can impact in my cancer journey.
- I have a sense of helplessness about the lymphoedema.
- I am bothered by my inability to control the lymphoedema.
- I often wish I could be normal again.
- I have the resilience to get through my lymphoedema treatment.
- I feel like it is my fault I have lymphoedema.

- I find the pace of progress frustrating.
- I am frustrated by the lack of predictability of the swelling.
- I feel unattractive because of the lymphoedema.
- I no longer like the way I look because of the lymphoedema.
- Lymphoedema makes me feel disfigured.
- I am not comfortable with dating or intimacy due to the lymphoedema.
- I worry about choking when I eat when I am swollen.
- I worry about the impact my swelling has on friends and family.
- I have no interest in dating/intimacy because of my lymphoedema.
- I am frustrated that my lymphoedema has not gone away.

Functional impacts

- My swallowing is difficult because of my lymphoedema.
- There are times of the day when my lymphoedema bothers me more than others.
- I put a lot of effort into managing my lymphoedema.
- I am unable to participate in activities because of my lymphoedema.
- I can’t eat the foods I want to eat because of my lymphoedema.
- I limit my social activities because of my lymphoedema.
- I prefer to stay at home because of my lymphoedema.
- When my lymphoedema is bad, I don’t want to do anything.
- Taking care of my lymphoedema is a lot of work.
- It is a struggle dealing with lymphoedema.
- My lymphoedema reminds me that I am dealing with a major health issue.
- I feel like I need to hide my lymphoedema with clothing.
- It is tiring having to explain my lymphoedema to others.
- I go to bed early because I am tired of dealing with my lymphoedema.
- I am constantly thinking about my lymphoedema.
- I can’t do some activities as long as I would like because of my lymphoedema.
- My lymphoedema impacts how I interact with others.
- I feel I can have some control over my lymphoedema.
- I try not to burden my family with my lymphoedema.
- I spend more time at home because of my lymphoedema.
- My facial expressions have changed because of my lymphoedema.
- Sometimes I stop talking because my speech changes with the swelling.
- I avoid mirrors because of my lymphoedema.
- I avoid seeing old friends because of the change in my appearance.
- I hide my lymphoedema with facial hair or clothing.
- People assume I have gained weight because of my lymphoedema.
- I cannot perform parts of my job because of my changed image.
- My work responsibilities have changed due to lymphoedema.
- I feel like I am constantly explaining lymphoedema to others.

- My lymphoedema forces me to disclose that I had cancer.
- I spend a good deal of my day doing something for the swelling.
- The swelling is on my mind all day, every day.
- I can take steps to control my swelling.
- My life is not normal because of the lymphoedema.
- I have to think hard about swallowing when I am swollen.
- I cannot enjoy meals with others because of my lymphoedema.
- I cannot hug friends and family the same way because of my lymphoedema.
- I go to bed early because I am tired of my lymphoedema.
- I avoid interacting with people because of my lymphoedema.
- I don't eat out because of my lymphoedema.
- I never know how my lymphoedema will be from day to day.
- I am constantly looking at and feeling my neck to see how the swelling changes.
- It is difficult to fit the lymphoedema treatment into my routine.
- I avoid intimate activities due to the lymphoedema.
- I think about where to sit at a table to limit how people will see my swelling.
- I avoid routine chores outside the house when I am swollen.
- People have difficulty understanding me when I am swollen.
- People have a hard time hearing me when I am swollen.
- It is difficult to shave/apply makeup when I am swollen.
- I don't drive when my neck is swollen.
- I cannot sleep in my bed due to the lymphoedema.
- I cannot sleep in my usual position due to the lymphoedema.
- I have to be careful about the foods I eat when I am swollen.
- I can only swallow liquids when I am swollen.
- I cannot eat and drink with normal utensils because of the swelling.
- People have a hard time interpreting my facial expressions because of the swelling.
- I can't lie on my back because of the lymphoedema.
- I don't go out because of my lymphoedema.

Physical impacts

- I feel uncomfortable with my lymphoedema.
- The unpredictability of my lymphoedema bothers me.
- Tightness in my skin makes the lymphoedema uncomfortable.
- Having lymphoedema is like having a monster around your neck.
- My voice doesn't sound normal when my lymphoedema is bad.
- My sleep is disrupted by my lymphoedema.
- I don't feel well rested because of my lymphoedema.
- It is hard for me to sleep because of my lymphoedema.
- I feel like my lymphoedema makes me look older than I am.
- It is physically difficult for me to manage my lymphoedema.

- The tightness of the lymphoedema can be unbearable.
- I am unable to turn my head comfortably because of the lymphoedema.
- When I wake up in the morning it is hard to move my neck because of the lymphoedema.
- I feel disconnected with parts of my body because of the lymphoedema.
- Dealing with my lymphoedema is exhausting.
- I look older because of my lymphoedema.
- I cannot perform parts of my job due to physical impacts of the swelling.
- I feel my lymphoedema every time I move my head.
- I am uncomfortable throughout the day due to the lymphoedema.
- I am always aware of the lymphoedema.
- I am exhausted at the end of the day because of my lymphoedema.
- My skin feels like it might tear due to the swelling.
- My lymphoedema makes me feel like I’m being strangled.
- It is hard to look down because of the swelling.
- Moving my head and neck is painful because of the swelling.
- The swelling impacts my facial expressions.
- My voice changes when I am swollen.
- My speech is unclear when I am swollen.
- It is physically difficult to talk when I am swollen.
- I have to use more effort to speak when I am swollen.
- My singing voice is impacted by my lymphoedema.
- It is hard to breathe when I am swollen.
- My lymphoedema impacts my sleep.
- It is difficult to drive because of my lymphoedema.
- It feels very stiff and solid under my chin.
- It is difficult to see clearly when I am swollen.
- I clear my throat a lot because of the swelling.
- My throat feels constricted.
- It is difficult to open my mouth when I am swollen.
- My hearing is worse when I am more swollen.
- My ears get clogged when I am swollen.
- I cannot swallow solids when I am swollen.
- My swallowing feels restricted when I am swollen.
- I cannot kiss as well due to my lymphoedema.

Appendix 3: Participant Information Sheet (PIS)

Participant Information Sheet (PIS)

NHS
Liverpool University Hospitals
NHS Foundation Trust

Head and neck lymphoedema patient reported outcomes

Summary:

This study has been designed to learn more about the patient experience with swelling after head and neck cancer treatment. This information will help our research team to develop an evaluation tool that clinicians can use to better understand how their patients are doing. This research is being performed as part of a PhD program and the interviewer you will meet with is a PhD student.

In this research study we will use information from you obtained during an interview. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. As the PhD student performing this research resides in the United States, your contact data will go outside of the United Kingdom/ European Union (UK/EU).

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules. This study has been reviewed and approved by the Wales Research Ethics Committee 4.

At the end of the study, we will save some of the data in case we need to check it. We will make sure no-one can work out who you are from the reports we write.

The information pack tells you more about this study.

You can find out more about how we use your data by:

- Emailing: Heather Starmer at h.starmer@liverpool.ac.uk
- Visiting: **www.hra.nhs.uk/patientdataandresearch**

We would like to invite you to take part in our research study.

- This study is being sponsored by the University of Liverpool.
- Before you decide, it is important to understand why the research is being done and what it will involve.
- The decision to participate is entirely up to you, but to help you decide we have put together this information sheet to give you a clearer idea of what is involved.
- We suggest you take a few minutes to read this leaflet.
- Please do feel free to talk to family and friends about the study.
- If anything is unclear at any point, please do ask as we are here to help you reach the decision that is right for you.
- You can withdraw your consent to participate in this study at any time.

Important things that you need to know.

- Head and Neck Cancer (HNC) is a general term that covers many different types of cancer.
- Head and neck lymphoedema is a type of swelling that can occur before or after cancer treatment.
- Different individuals have different experiences with head and neck swelling.
- We want to find out how head and neck swelling impacts individuals who have been through cancer care.
- Participants will be asked to participate in an interview over video conference to talk about their experience with head and neck swelling.

Why is the study needed?

Many patients who are treated for head and neck cancer develop a specific type of swelling called lymphoedema. This swelling can lead to issues with eating, speaking, and breathing as well as impact how a person feels about their appearance. There are treatments that can help to reduce this swelling, however we need better ways to document how this swelling impacts individuals and how well different treatments work. This study is focused on getting a better understanding of how lymphoedema impacts people who have been treated for head and neck cancer in order to guide the creation of a patient reported outcome tool. Such a tool will allow clinicians to get a better understanding of how swelling impacts an individual in order to determine the most appropriate treatment.

What does taking part in this study involve?

Taking part in this study would require you to:

- Participate in a single interview via Zoom. Once you indicate interest in participating our team will reach out through email to set up an interview time and date. We will then provide you with instructions on how to login to the zoom meeting. This interview will last 30 minutes to 1 hour in duration. This will involve answering questions regarding your experience of head and neck swelling.
- Before the interview begins, you will be asked to give verbal consent.
- This interview will be audio recorded to allow for transcription of the interview. The recording will then be deleted following transcription and will not be shared or used for any other purposes.
- This interview will remain confidential and will not be shared.
- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

Why am I being asked to take part, and am I eligible?

We are inviting individuals who have experienced head and neck swelling to share their experiences.

You are eligible to take part in the study if you:

- Are aged 18 or over.
- Have been diagnosed with head and neck cancer.
- Have been diagnosed with swelling of the head and neck (lymphoedema).
- Have access to an electronic device (i.e. laptop/computer or smart phone) to attend a video interview.

- Speak good English.

You are not eligible to take part in the study if you:

- Do not have a diagnosis of head and neck lymphoedema.

What are the possible benefits of taking part?

This study will not provide any immediate benefit to you if you participate. However, this study aims to evaluate your experience to develop a tool to measure the patient perspective around head and neck swelling. This will potentially benefit future patients because the results may influence the future services we provide to patients in their cancer journey.

What are the possible disadvantages and risks of taking part?

There are no immediate risks to your safety from your participation in this study. Taking part will not influence the continued treatment and follow up you receive. Recalling your cancer experience may be upsetting but we will listen to and be sensitive to your needs.

If you have any worries regarding this study, please contact and speak to the research team. We will be happy to try and explain and resolve any problems. If you are still not happy, then you can make a formal complaint through the Patient Advice and Liaison Service (PALS). Aintree Hospital has a dedicated PALS team who deal with comments, concerns, and complaints. The team will listen to you, respond in a timely manner and learn from you to help improve our services. You can contact PALS by visiting their helpdesk on the ground floor of Aintree Hospital directly or by:

Telephone: 0151 529 3287
Email: customerservice@aintree.nhs.uk

Appendix 4: Consent form (United States)

DESCRIPTION: You are invited to participate in a research study on the experience of individuals with head and neck lymphedema. Our goal is to better understand the experience of patients with lymphedema in order to develop a patient reported outcome tool. You will be asked to answer a series of questions about your personal experience and your answers will be recorded and later transcribed. Once the recordings are transcribed, they will be destroyed. None of your personal identifying information will be collected or recorded.

TIME INVOLVEMENT: Your participation will take approximately 30-60 minutes.

RISKS AND BENEFITS: The risks associated with this study are limited only to your possible discomfort in answering questions. If there are any questions you prefer not to answer, it is fine to decline. We cannot and do not guarantee or promise that you will receive any benefits from this study. Your participation may benefit future patients with head and neck lymphedema. Your decision whether or not to participate in this study will not affect your care.

PAYMENTS: There will be no payments associated with this research.

PARTICIPANT'S RIGHTS: If you have read this form and have decided to participate in this project, please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. The alternative is not to participate. You have the right to refuse to answer particular questions. The results of this research study may be presented at scientific or professional meetings or published in scientific journals. Your individual privacy will be maintained in all published and written data resulting from the study.

CONTACT INFORMATION:
Questions: If you have any questions, concerns or complaints about this research, its procedures, risks, and benefits, contact the Protocol Director, Heather Starmer at 650-529-5903.

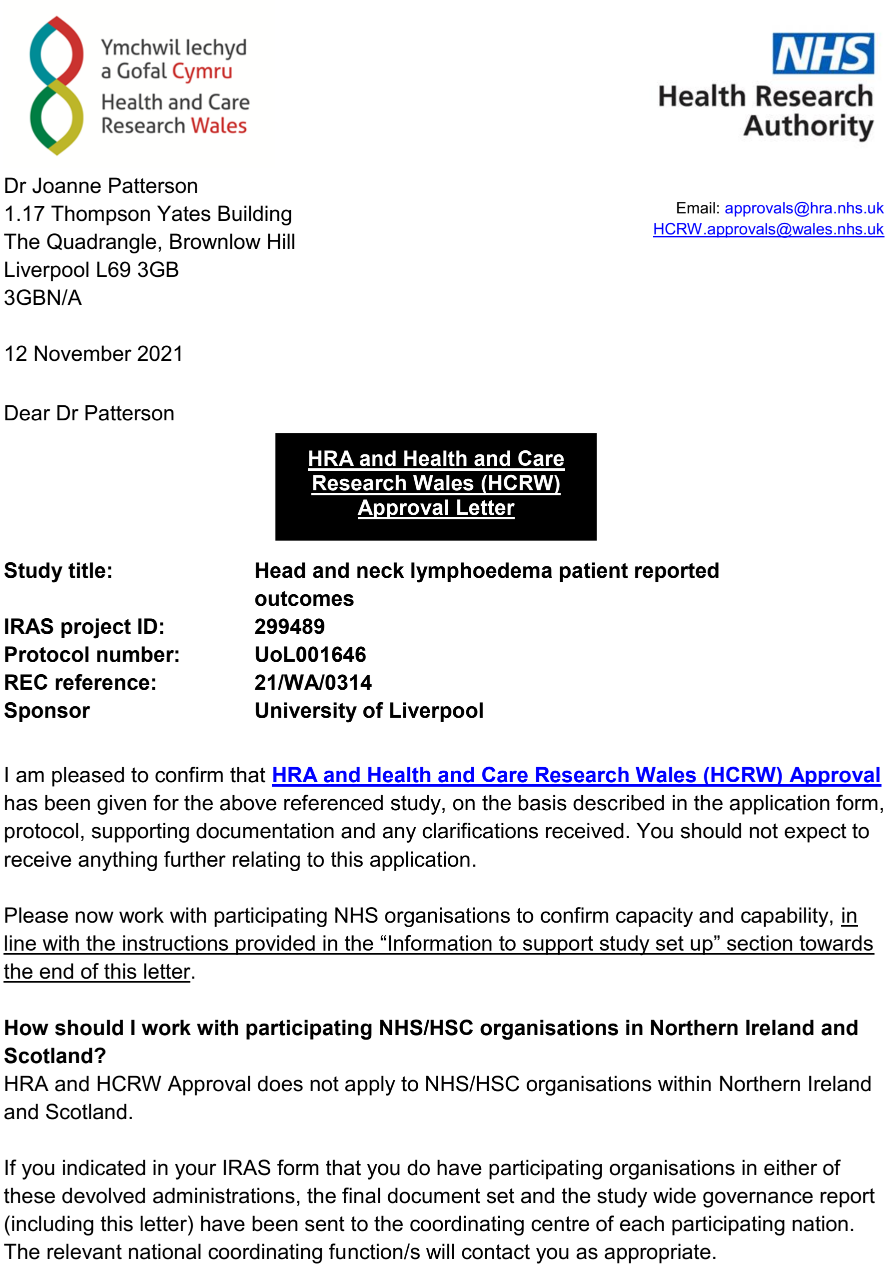
Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-2480 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

With your permission, the interview will be audio taped. If you do not wish to be audio taped, please indicate this to the researcher.

With your permission, the tapes from this study will be used for transcription of the conversation. If you do not agree with this, please indicate this to the researcher.

If you agree to participate in this research, please indicate this to the researcher.

Appendix 5: Ethical Approval (UK)



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales

NHS
Health Research
Authority

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

Dr Joanne Patterson
1.17 Thompson Yates Building
The Quadrangle, Brownlow Hill
Liverpool L69 3GB
3GBN/A

12 November 2021

Dear Dr Patterson

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Head and neck lymphoedema patient reported outcomes**
IRAS project ID:	**299489**
Protocol number:	**UoL001646**
REC reference:	**21/WA/0314**
Sponsor	**University of Liverpool**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

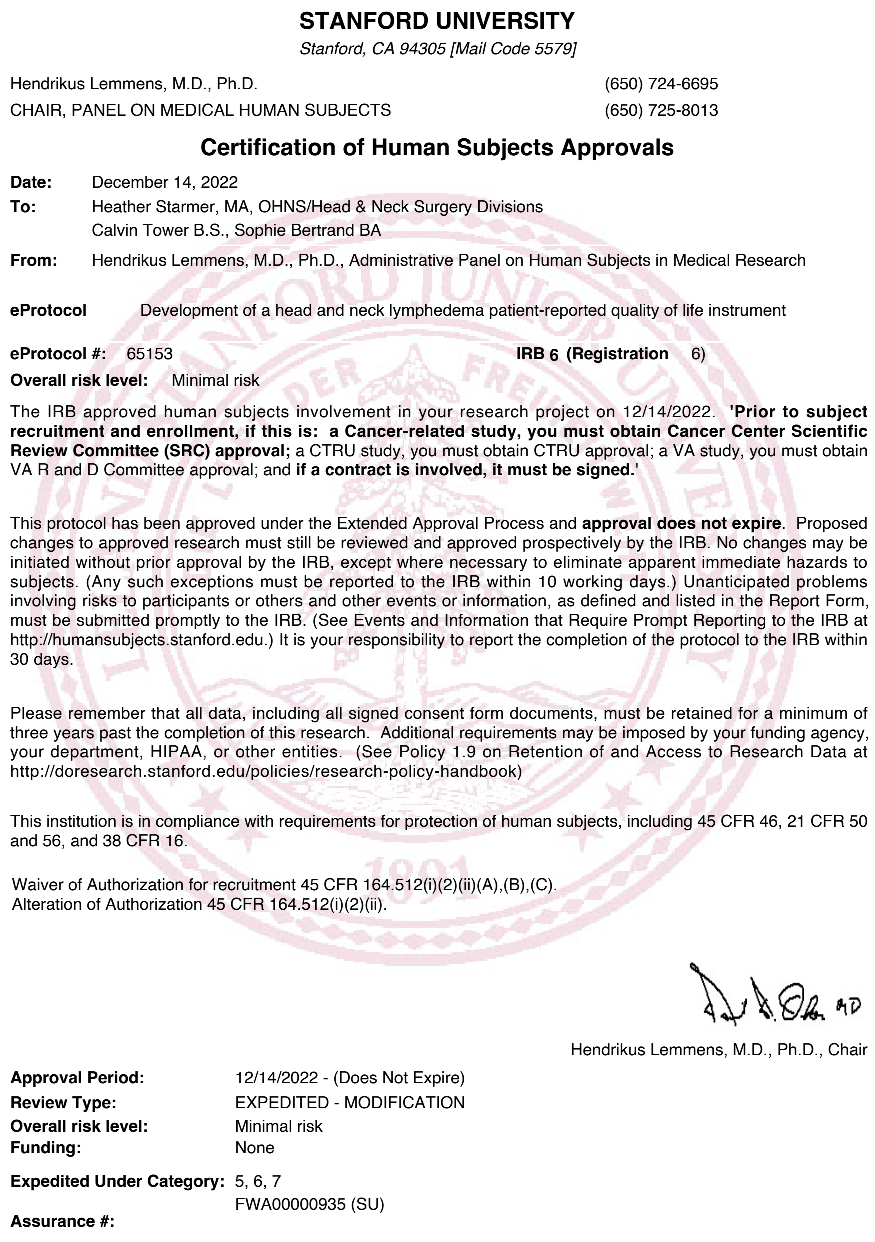
Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix 6: Ethical approval (US)



STANFORD UNIVERSITY
Stanford, CA 94305 [Mail Code 5579]

Hendrikus Lemmens, M.D., Ph.D. (650) 724-6695
CHAIR, PANEL ON MEDICAL HUMAN SUBJECTS (650) 725-8013

Certification of Human Subjects Approvals

Date: December 14, 2022
To: Heather Starmer, MA, OHNS/Head & Neck Surgery Divisions
Calvin Tower B.S., Sophie Bertrand BA
From: Hendrikus Lemmens, M.D., Ph.D., Administrative Panel on Human Subjects in Medical Research

eProtocol Development of a head and neck lymphedema patient-reported quality of life instrument

eProtocol #: 65153 **IRB 6 (Registration** 6)
Overall risk level: Minimal risk

The IRB approved human subjects involvement in your research project on 12/14/2022. **'Prior to subject recruitment and enrollment, if this is: a Cancer-related study, you must obtain Cancer Center Scientific Review Committee (SRC) approval;** a CTRU study, you must obtain CTRU approval; a VA study, you must obtain VA R and D Committee approval; and **if a contract is involved, it must be signed.**'

This protocol has been approved under the Extended Approval Process and **approval does not expire**. Proposed changes to approved research must still be reviewed and approved prospectively by the IRB. No changes may be initiated without prior approval by the IRB, except where necessary to eliminate apparent immediate hazards to subjects. (Any such exceptions must be reported to the IRB within 10 working days.) Unanticipated problems involving risks to participants or others and other events or information, as defined and listed in the Report Form, must be submitted promptly to the IRB. (See Events and Information that Require Prompt Reporting to the IRB at http://humansubjects.stanford.edu.) It is your responsibility to report the completion of the protocol to the IRB within 30 days.

Please remember that all data, including all signed consent form documents, must be retained for a minimum of three years past the completion of this research. Additional requirements may be imposed by your funding agency, your department, HIPAA, or other entities. (See Policy 1.9 on Retention of and Access to Research Data at http://doresearch.stanford.edu/policies/research-policy-handbook)

This institution is in compliance with requirements for protection of human subjects, including 45 CFR 46, 21 CFR 50 and 56, and 38 CFR 16.

Waiver of Authorization for recruitment 45 CFR 164.512(i)(2)(ii)(A),(B),(C).
Alteration of Authorization 45 CFR 164.512(i)(2)(ii).

MD

Hendrikus Lemmens, M.D., Ph.D., Chair

Approval Period: 12/14/2022 - (Does Not Expire)
Review Type: EXPEDITED - MODIFICATION
Overall risk level: Minimal risk
Funding: None

Expedited Under Category: 5, 6, 7
Assurance #: FWA00000935 (SU)

Appendix 7: Co-author permission to include articles in thesis

As a co-author of the following studies, I give permission for Heather Starmer to include these publications in her thesis entitled “Assessment of head and neck lymphoedema: The importance of the patient perspective.”

- Starmer HM, Cherry MG, Patterson J, Young B, Fleming J. (2023). Assessment of measures of head and neck lymphedema following head and neck cancer treatment: A systematic review. *Lymphatic Research and Biology*. 21(1): 42-51.
- Starmer HM, Patterson J, Fleming J, Cherry MG, Young B. (2023). Head and neck lymphedema and quality of life: The patient perspective. *Supportive Care in Cancer*. 31(12): 696.
- Starmer HM, Patterson J, Young B, Fleming J, Cherry MG. (2024). Development of an head and neck lymphoedema specific quality of life tool: The Comprehensive Assessment of Lymphoedema Impact in the Head and Neck (CALI-HaN). *Head and Neck.*

J. C. Fl

M. Gemma Cherry

Jason Fleming

Bridget Young

Joanne Patterson

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