Patient-Centred Outcomes in Head and Neck Oncology

by

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ABSTRACT

Cancers in the head and neck often lead to disability in basic functions, including speech and swallowing. Restoration of these functional impairments is the main treatment goals in managing patients affected by head and neck cancer. Historically, expert stakeholders including clinicians and researchers determine the outcomes measured. Increasingly, it is now believed that these conventional outcomes measures do not provide all the information needed to fully capture treatment effects. Incorporation of patient perspectives, or patient-reported outcomes (PRO), in functional outcome measures has been gaining increasing prominence in the reconstructive literature. The objective of this study was to create and validate the first instrument to measure the main functional areas of concern of the head and neck oncology patient. This was a four-phase qualitative study. In Phases I and II, function domains of importance were identified using open-ended questioning of head and neck cancer patients and grounded theory. The itemized PRO (i.e., Head and Neck Research Network-33) was created in Phase III with expert and patient input. In the final phase, patients completed the Head and Neck Research Network-33 (HNRN-33) as well as completed modified barium swallow testing, speech intelligibility (SI) testing, MD Anderson Dysphagia Inventory, and the European Organization for Research and Treatment of Cancer (EORTC) quality of life head and neck questionnaire in order to perform criterion validity testing. The HNRN-33 correlated strongly with assessments of swallowing (0.77, -0.73, and -0.60). Similarly, strong correlations were observed between the HNRN-33 and assessments of speech (-0.64, 0.61, and 0.55). Assessments of dry mouth and chewing domains correlated moderately to strong, with observed *r* values of -0.54 and -0.45, respectively. A factor analysis was

also performed using multi-institutional data. The factor loading values for the domains of swallowing, speech, dry mouth, and chewing were all observed to be greater than 0.3 with p-values < 0.001. The mean factor loading values for the items relating to swallowing and speech were 0.71 and 0.76, respectively. The mean factor loading values for the items relating to dry mouth and chewing were 0.71 and 0.77, respectively. These values represent very strong loading values between the individual items and their respective domains. The HNRN-33 is the first validated patient-reported outcome instrument designed to assess functional outcomes in head and neck oncology patients and could serve as a single comprehensive measure for functional outcomes. Future research may entail attempting to validate the HNRN-33 as a screening tool for functional assessment in head and neck cancer patients.

PREFACE

Ethics approval was attained for this study in Canada from the University of Alberta Research Ethics Board (REB, reference number Pro00046886_AME3).

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I would like to thank my supervisors, Dr. Hadi Seikaly and Dr. Dean Eurich, as well as my entire supervisor committee for the help and guidance they have provided me during my research endeavors. Your insightful and timely advice helped me navigate through the complex work of academia. Finally, I would like to thank my family for their unwavering support, which I needed more than I let you know.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 PATIENT-CENTRED OUTCOMES RESEARCH

In the field of clinical medicine, treatments are compared to one another by measuring their effect on a set of predetermined *outcomes*. The study of treatment comparison, in terms of benefits and harms, is known as comparative effectiveness research (CER).[1] Historically, expert stakeholders including clinicians and researchers have determined these measured outcomes. However, it is now believed that these conventional outcomes do not provide all the information needed to understand treatment effects.[1]

There has been a shift towards incorporation of patient perspectives in the outcomes literature.[2] Modern health care is patient-centric, where patients and their families are encouraged to actively participate in decision making. A comprehensive treatment evaluation is now believed to include patients' perspectives of treatments in terms of the patients' actual experiences (e.g., functional impact).[1] This shift in the medical community's attitude towards patient involvement in health care decision making has led to the further development of the scientific field known as patient-centred outcomes research (PCOR). In its most basic definition:

> [PCOR] is research that is informed by the perspectives, interests, and values of patients throughout the research process, from the selection of research questions to the dissemination of research results. PCOR is intended to be practically relevant. Its real-world impact on patients is known and included in decisions about prevention, diagnosis and treatment.[3]

A natural extension of PCOR is the idea of a patient-reported outcome (PRO). Many important outcome measures are not easily assessed objectively, including outcomes such as chewing and pain. When attempting to measure subjective outcomes, these are best

reported by patients themselves and are formally known as PROs. Furthermore, there exists "some outcomes that cannot reliably and accurately be assessed by any means other than direct patient report, so inclusion of PROs is often essential to patient-centeredness."[4] Although the previous statement can be applied to many disciplines of medicine, it holds special importance in head and neck oncology as the majority of reported outcomes are patient specific (e.g., chewing, taste).

1.2 HEAD AND NECK ONCOLOGY AND PATIENT-CENTRED OUTCOMES RESEARCH

The global impact of head and neck cancer on function can be significant and is often related with poor quality of life outcomes. [5] Along with survival, functional outcomes are of high priority to cancer patients and are relevant when considering treatment strategies.[6] Assessment of functional outcomes in head and neck oncology is multidimensional, with broad subjective domains, including fatigue, weakness, and walking difficulty among others.[5] PROs can translate these patient experiences to measureable outcome scales in a more accurate manner than conventional assessment tools. Furthermore, as functional outcomes are important parameters in head and neck cancer research, using PROs would allow for more standardized, accurate outcome assessment of head and neck treatments. PROs additionally have the advantage of being accessible to all health care professionals, allowing this type of outcome measurement to be universal.

1.3 STUDY OBJECTIVES

The primary objectives of this thesis were to:

1. Identify the main functional domains of interest to head and neck cancer patients, and

2. Develop and validate a single assessment instrument to measure the main mechanical functional domains of interest to head and neck cancer patients.

These objectives are achieved through a series of inter-related summaries and studies. In Chapter 2, the history of comparative effectiveness research (CER) will be discussed and how this led, in part, to the evolution of PCOR. A further discussion on the importance of PCOR and its beneficial role in the functional outcomes of head and neck oncology will then follow. In Chapter 3 through a systematic review of the literature, I will present and discuss PRO models that have been developed for functional assessment of head and neck cancer patients. Through a mixed-methods study presented in Chapter 4 and 5, the main functional domains of interest to head and neck cancer patients are identified followed by the development of a novel instrument to measure these domains (Head and Neck Research Network-33). A multi-institutional validation study of the Head and Neck Research Network-33 will then be discussed in Chapter 6. Finally, a summary of my findings and future directions for PCOR in head and neck cancer patients are provided in Chapter 7.

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CHAPTER 2: BACKGROUND

2.1 COMPARATIVE EFFECTIVENESS RESEARCH

> CER [comparative effectiveness research] is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.[1(p203)]

This definition, proposed by the Institute of Medicine in the United States in 2009, highlights an important concept in medical decision making, although the concept itself is not new. The idea of comparative medicine has been implemented for several decades, primarily by the pharmaceutical industry and private sector, motivated by capital gain.[2] The concept of comparative medicine has also gained traction in many areas of medicine as clinicians and researchers search for the best evidence-based therapeutic option to treat their patients. Particularly in the field of head and neck oncology, where debate remains regarding whether primary surgery or radiation offers best outcomes, researchers have been publishing treatment outcome studies for several years.[3-5]

Recently, there has also been a significant increase in federal attention to this type of research in the United States and the subsequent funding available. In 2009, under the American Recovery and Reinvestment Act, the United States pledged $1.1 billion to support comparative effectiveness research. A large component of the American Recovery and Reinvestment Act is to "involve patients and their caregivers in key aspects of CER, including strategic planning [and] priority setting,"[1(p204)] a radical idea that spurred the creation of the Patient-Centered Outcome Research Institute, which will be further discussed in the next section. [1] In other countries such as Canada, further

investments are also being made in CER. Recently in 2014, the Canadian Clinical Trials Coordinating Centre was created to implement an action plan that includes measuring and monitoring clinical trial performances.[6]

With new federal funding in North America, it appears that the future of CER is secure. Overall, the benefit of CER to patients and clinicians is tremendous, as it allows informed decision making while choosing treatment modalities. Additionally, it also allows health care institutions and federal programs make more informed decisions regarding which treatment avenues to fund.[7] This renewed importance in CER has also naturally transitioned to the evolving discipline of patient-centred outcome research.

2.2 PATIENT-CENTRED OUTCOMES RESEARCH

In March of 2010, President Barack Obama signed a landmark health care reform bill that created the non-profit organization known as the Patient-Centered Outcomes Research Institute (PCORI). [8] As a direct extension of CER's goal of involving patients and caregivers in the prioritization of health care outcomes, PCORI was mandated to promote "evidence-based information that comes from research guided by patients . . . [and to focus on] providing useful information about the outcomes that are important to patients."[9(pi)] With funding in the realm of $500 million per year, PCORI and PCOR are firmly in the health agenda in the United States. Canada has also followed suit with the formation of the Strategy on Patient-Oriented Research in 2010, a national funded organization. This shift in the prioritization of PCOR in North American health care is a beneficial change for patients, clinicians, and expert stakeholder. Over the next few paragraphs, a review is presented related to how PCOR is capable of: (1) attaining a

standardized outcome measure when the patient perception is the gold standard (e.g., pain, taste), (2) creating outcome measures that are universally accessible to all clinicians, and (3) prioritizing outcomes in order to have a single assessment tool in place of a battery of functional outcome tests.

It has been recognized that patients view outcomes of treatments differently than researchers.[10] In the rheumatology literature, it has been shown that patients view fatigue as an important outcome, despite fatigue traditionally not being a readily measured outcome in that discipline.[11] This "patient perspective" has, therefore, become an integral part of outcome assessments in rheumatology as well as in other disciplines of medicine. As in the example of fatigue, the outcomes prioritized by patients often highlight individual experiences that may not lend easily to being assessed by traditional measurement tools (e.g., x-ray imaging, blood tests, etc.). This requires a greater reliance on PROs, as this form of assessment captures information best reported by patients themselves.[9] An additional important advantage of PROs is that they are capable of being administered easily and at relatively low costs.

The inherent attribute of PROs being a form of a questionnaire allows the cost associated with it to be minimal as compared to traditional assessment tools such as modified barium swallow or computer-tomography imaging. These latter examples require not only a significant upfront cost of the instrument itself, but also significant maintenance and administrative costs, as they require trained technicians to operate. The transportability, negligible cost, and ease of administration truly make PROs a measurement tool accessible to all clinicians and stakeholders involved in health care. This also allows PROs to be used in comparative effectiveness research universally.

The most significant benefit of PCOR is its ability to prioritize outcomes to be measured. The experience by the outcome measures in rheumatology (OMERACT) group highlights this point. As several outcome metrics exist with a myriad of instruments for evaluating these outcomes, the OMERACT group found that there existed no consensus as to which outcomes and tools to use, with different research groups reporting different outcomes and using different tools. This created significant difficulty in comparing treatments and outcomes between different research publications. OMERACT looked to patients for prioritizing which outcome areas to measure routinely. This permitted for an eventual agreement on a *core set* of outcomes to be measured universally and routinely in rheumatology. This was an instrumental move for advancing CER in rheumatology. Potential applications of this framework exist in many other areas of medicine. As stated previously, this has particular relevance in head and neck oncology, where numerous functional outcomes and instruments exist, posing the same difficulty in CER as was experienced by the OMERACT group in rheumatology. [12] In the next section, an overview of current assessment methods of functional outcomes in head and neck oncology is provided.

2.3 FUNCTIONAL OUTCOMES IN HEAD AND NECK ONCOLOGY

The primary treatment goal of head and neck cancer is survival, but nearly as important because of the global impact head and neck cancer has on function is achieving high functional outcomes for patients undergoing treatment. [13] The assessment of functioning in head and neck cancer patients is, therefore, important for well-being as well as the advancement of head and neck treatment through CER. Here, a brief overview is presented of the current functional outcome assessment models that are used in the

literature, and I will further analyze the difficulty in the assessment of functioning in head and neck cancer.

In 2008, Mylnarek et al. published a review article of various methods of functional outcome assessments used in the oral and oropharyngeal cancer literature. [14] The authors identified 60 studies that used measurement tools principally for the assessment of speech and swallowing, noting that the types of measurement varied drastically between the studies. Objective assessment methods for swallowing included videofluoroscopic swallowing studies, scintigraphy, tongue strength measurements, computed tomography, endoscopic assessments of swallowing, and chest radiography. Speech was assessed using acoustic and aerodynamic parameters as well as perceptual analysis. Other studies chose to assess function using various quality of life questionnaires, including the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaire, the H&N35, the Performance Status Scale for Head and Neck Cancer, the University of Washington Quality of Life questionnaire, and the M.D. Anderson Dysphagia Inventory among many others. Similarly, in 2003 Stier-Jarmer et al. published a review of functional outcome assessments in head and neck cancer and identified 146 patient-reported outcome measurements as well as 64 other assessment tools rated by health professionals.[15] These functional outcomes assessed various domains of function, including quality of life, food intake, pain, speech, and breathing, as well as psychosocial functioning.

Illustrated by these two previous review articles, the choice of *what* functional outcome to assess and *how* to assess it was extensive. This creates a significant challenge when comparing treatment modalities for head and neck cancer, as different research centres

have chosen to report different outcomes. Recently, there has been an effort to standardize which outcome measures to report in head and neck cancer. A widely used method to accomplish this task is identifying a core outcome set, which refers to outcomes that should be consistently measured and reported in clinical trials. [16] Tschiesner et al. proposed the development of a core outcome set in head and neck cancer within the context of the International Classification of Functioning (ICF)-Disability and Health.[17] The ICF is based on an integrative biopsychosocial model of functioning, disability, and health. From over 1,400 categories in the ICF, Tschiesner et al. identified 19 to comprise the core set for head and neck cancer. Similarly, in 2014 Waters et al. presented a protocol to establish a core outcome set for oropharyngeal-specific cancer, in an attempt at outcome standardization.[16]

The attempt at standardization of outcomes in head and neck oncology by research groups is indicative of the widely recognized necessity of a core set of outcomes to allow efficient treatment comparisons universally. The groups of Tschiesner et al.[17] and Waters et al.[16] have presented global outcomes assessments of head and neck cancer, including and encompassing psychosocial domains. While this psychosocial domain is certainly needed, our research group is instead focused solely on mechanical functional outcomes. We have chosen to concentrate on this specific subset, as the primary objective of this study is to develop a single assessment tool. By limiting the scope of the assessment tool to measure only mechanical functional outcomes, we would be able to create a questionnaire of appropriate length that would not incur significant patient or practitioner burden.

PCOR is suited to many disciplines of medicine and, in particular, has the potential to benefit the field of head and neck oncology. In the PCOR section, it was stated that PCOR has the ability to prioritize outcome measures and has been utilized in this form by several disciplines, including rheumatology.[12] Furthermore, as the majority of the mechanical functional outcomes in head and neck cancer are best interpreted by the patient (e.g., chewing, taste), the use of PROs is essential. The literature for current use of PROs is now reviewed, displaying both content and construct validity in head and neck oncology.

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CHAPTER 3: PATIENT-REPORTED OUTCOMES IN HEAD AND NECK ONCOLOGY: A SYSTEMATIC REVIEW

3.1 INTRODUCTION

Published literature in numerous medical disciplines affirmed that patients view outcomes of medical interventions differently than researchers. [1] As such, this impacts the reporting of treatment outcomes. Varied medical fields have incorporated this patient perspective as an integral part of their outcome measures.[1] Researchers in rheumatology have recently established fatigue and disturbed sleep were important outcomes to rheumatoid arthritis patients—two domains that had not previously been evaluated extensively. This spurred numerous studies pertaining to the development of validated outcome measures for these domains.[2]

In 2012, the Patient-Centered Outcomes Research Institute (PCORI), appointed by congress in the United States of America, published a methodology report on performing valid patient-centred outcomes research (PCOR).[3] According to PCORI, this outcome format should involve subjective reporting by the patient (i.e., questionnaires). This is formally known as a patient-reported outcome (i.e., subjective reporting by the patient). Each patient-reported outcome (PRO) is also required to demonstrate that patients have been included in the actual development process in order to be valid.[3]

The field of head and neck cancer surgery has made strides in the past decade to advance patient-centred outcomes research. A systematic review of PRO instruments that measure quality of life in head and neck cancer surgery was published in 2007, which identified 12 questionnaires in the literature that met criteria of a PRO.[4] In 2008, Kanatas and

Rogers published a complete guide to all questionnaires used in health-related quality of life in head and neck oncology.[5] They identified 13 head and neck specific questionnaires and seven head and neck function questionnaires in the literature, indicating a fairly diverse breadth of PRO measures in head and neck oncology.[5] Although these reviews have helped to summarize the publications relating to PROs in head and neck oncology, they have not assessed the validity of any of these instruments. Therefore, the merit of these instruments is unknown.

The purpose of this systematic review was to determine if validated PRO instruments to measure function in head and neck oncology patients existed in the literature. In a separate study, the authors of this paper have identified swallowing, speech, dry mouth, and chewing as the domains of function that head and neck patients prioritize. Therefore, this review will focus on instruments that assess these functional domains.

3.2 METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2.1 Literature search

A search of the literature was conducted using MEDLINE, EMBASE, and the Cochrane databases. The search timeline spanned from the inception of the databases up to June 22, 2016. The objective of this literature search was to identify all PRO instruments measuring swallowing, speech, dry mouth, and chewing in head and neck oncology patients. Once identified, we then analyzed the instruments for validity using a filter

developed by the US Food and Drug Administration (FDA). No protocol for this systematic review has been previously published.

3.2.2 Inclusion criteria

We reviewed all English language, published, peer-reviewed abstracts identified from our search strategy. All abstracts using patients $\geq$ 18 years of age were considered.

Adrian Mendez and Hadi Seikaly independently reviewed all abstracts. A third reviewer, Dean Eurich, resolved any discrepancies between the two reviewers. Studies using PRO instruments that were not in the form of a questionnaire or survey were not considered. Squamous cell carcinoma represents approximately 95% of all malignant cancer of the head and neck and, due to its aggressive nature, represents a unique clinical entity. Studies that did not exclusively use head and neck squamous cell carcinoma patients in their development were eliminated as were studies that did not use instruments measuring at least one functional domain of swallowing, speech, chewing, or dry mouth. Finally, studies that did not detail the development process of the instrument were also eliminated.

The full-text studies of the remaining abstracts were retrieved and reviewed by Adrian Mendez and Hadi Seikaly. If an article referenced a prior study that described the development process of the instrument, these studies were also reviewed.

3.2.3 Data extraction

Study characteristics including authors, journal of publication, publication date, and study title were recorded and tabulated. Although no gold standard exists for the evaluation of PRO instruments, the US FDA and the OMERACT, which are leaders in PRO, have each

developed filters for this purpose. The filter OMERACT uses is based upon that developed by the US FDA. For the purpose of our review, we used a modification of the original filter developed by the US FDA.[6] In reviewing the full text studies, we focused on four properties of each instrument: (1) reliability, (2) content validity, (3) construct/ criterion validity, and (4) ability to detect change.

3.2.4 US FDA PRO instrument filter

The modification of the US FDA PRO instrument filter specifically analyzed for reliability, content validity, construct/criterion validity, and ability to detect change. [6] In assessing the reliability of each PRO instrument, we identified if appropriate reliability tests were conducted on the instrument, and if so, what statistical tests were used. Commonly used reliability tests are internal consistency, inter-reviewer reproducibility, and test-retest.

In our assessment of validity, we identified whether the PRO instruments had content and construct validity. Content validity was assessed by reviewing the instrument development process and identifying whether the following had been met: (1) head and neck cancer patients had been used, (2) expert/literature review was undertaken, and (3) cognitive interviewing had been employed. Reviewed PRO instruments were deemed to have construct validity only if they used statistical tests to demonstrate one of discriminant, convergent, or known-groups validity.[6]

In assessing whether an instrument has the ability to detect change, instrument scores should demonstrate a change in the predicted direction when there has been a notable

change in the patient (i.e., response to treatment). Conversely, PRO instrument scores are expected to remain stable when no change has been demonstrated in the patient.[6]

3.2.5 Instrument attributes

The following attributes of each PRO instrument we analyzed were collected: intended use of the measure, concepts measured, number of items, intended measurement population or condition, mode of data collection, timing and frequency of administration, types of scores, weighting of items or concepts, and response options.

3.2.6 Statistical analysis

Summary reliability and validation statistics were abstracted for each study if reported. For reliability, this included test-retest and internal consistency statistics. Abstracted validity statistics included correlation tests as well as factor analysis.

3.3 RESULTS

After removing duplicated abstracts, our literature search of Medline, EMBASE, and the Cochrane databases identified 627 abstracts. Of these, 604 abstracts were excluded because they did not measure domains of function or did not use head and neck cancer patients in their PRO development. Twenty-three studies were identified for full article review. After review, a further 21 were excluded, as they did not specifically use head and neck squamous cell carcinoma patients in the PRO development or did not measure functional domains that included at least one of speech, swallowing, chewing, or dry mouth. In total, two studies were included in the final analysis (Figure 3-1).

3.3.2 Study characteristics

Our search identified two studies that met inclusion criteria. The study characteristics are described in Table 3-1. Both studies described the development and validation of questionnaires that measured function.

The first study pertained to a questionnaire to address swallowing function while the second study described a questionnaire to measure xerostomia. Both instruments were developed with the use of head and neck cancer patients. The first study took place in the United Kingdom, while the second study was based in Ann Arbor, Michigan.[7,8]

3.3.3 Govender et al.: Swallowing outcome after Laryngectomy Questionnaire[7]

The objective of this study was to develop and validate a laryngectomy-specific questionnaire to investigate swallowing function. This was a two-phase study, describing first the development and then the validation of the questionnaire.

During development of the Govender et al. questionnaire, two separate focus groups were organized involving six speech language therapists and 10 laryngectomy patients.[7] Although implied, it was not directly stated whether the patient population was composed of all head and neck cancer patients, as there was no discrete inclusion or exclusion criteria. Themes from the focus groups were then generated and then categorized using the WHO International Classification Framework.[7] These were then used to create the questionnaire. Cognitive interviewing was then performed on 10 laryngectomy patients, and further questionnaire modifications were subsequently made. The final version of the Swallowing Outcome after Laryngectomy (SOAL) was a 17-item questionnaire.

Validation of the questionnaire was then performed by administering the questionnaire to three distinct group of patients (i.e., laryngectomy: $N = 19$; radiotherapy: $N = 19$; healthy: $N = 20$). Internal consistency was measured using Cronbach's alpha for all three groups and laryngectomy patients alone ($\alpha = 0.96$ and $\alpha = 0.91$, respectively). The authors were able to show validity of their instrument by showing that different population groups (i.e., laryngectomy, radiotherapy, and healthy) scored differently on the SOAL. Furthermore, they showed correlation between the SOAL scores and modified barium swallow, which is an objective assessment of swallowing (Table 3-2).

3.3.4 Eisbruch et al.: Xerostomia Questionnaire[8]

The objective of this study was to develop an instrument to assess long-term xerostomia in patients receiving radiation therapy for head and neck cancer. During item development of the Xerostomia Questionnaire (XQ), the authors performed a literature search of xerostomia-specific and general head-and-neck-cancer quality of life instruments. They also completed surveys of patients and engaged in discussions with members of the Head and Neck Oncology Program at the University of Michigan. Based on their study, Eisbruch et al. implied that the surveyed patients were previously radiated head and neck cancer patients, although no specific comments were made about diagnosis or treatment. No indication was given of how many patients were surveyed or the specifics of the survey. An eight-item questionnaire was developed, with the final summary score ranging from 0 to 100. No cognitive interviewing was undertaken.

Validity and reliability statistics were generated by administering the XQ to 132 head and neck cancer patients undergoing radiation therapy. Eighty-four patients received bilateral neck full term radiotherapy (RT), while 48 received unilateral neck RT. The XQ was

administered at seven time points, which included pre-RT and at 1, 3, 6, 12, 18, and 24 months post-RT. Reliability of the instrument was evaluated using test-retest correlation and by measuring internal consistency using Cronbach's α (Table 3-2). Construct validity was first demonstrated by known-groups validity. At all time points, the bilateral neck RT group had significantly higher XQ scores than the unilateral neck RT group. Furthermore, criterion validity was demonstrated by correlating the XQ scores to the dichotomous xerostomia instrument summary scores. At baseline and at one-month post-RT, the two instruments were highly correlating with Spearman correlation coefficients (r) of 0.73 ($p < 0.01$), and 0.84 ($p < 0.01$), respectively (Table 3-2).

3.4 DISCUSSION

The global impact of head and neck cancer on function is profound and often results in adverse quality of life outcomes.[9] Along with survival, functional outcomes are of high priority to cancer patients and are relevant when considering treatment strategies.[10] Assessment of functional outcomes in head and neck oncology is multidimensional, with broad subjective domains including fatigue, weakness, and difficulty with walking among others.[9] PROs can translate these patient experiences to measureable outcome scales in a more accurate manner than conventional assessment tools. Furthermore, as functional outcomes are important parameters in head and neck cancer research, using PROs would allow for more standardized, accurate outcome assessment of head and neck treatments in the literature.

Although it would appear there are an abundance of questionnaires and PROs used in the field of head and neck cancer surgery, almost all of these lack a crucial developmental

process—inclusion of patients in their inception. Multiple organizations specializing in patient-centred outcome research (PCORI, FDA, PROMIS, and OMERACT) underline the importance of including the specific patient population, which was tested in the actual development of the PRO.[1,3,6] Without the use of head and neck cancer patients during development, PROs in the field of head and neck cancer surgery cannot be considered valid, despite undergoing validation studies.

From previous studies, it is known that the domains of function that head and neck cancer patients consider the most important are swallowing, speech, chewing, and dry mouth.[10] In their 2013 study, Rogers et al. looked at what outcomes head and neck cancer patients considered significant.[10] The authors noted that what patients considered most important varied depending on tumor site and progression of the disease. However, four outcomes remained consistent, and these included speech, swallowing, chewing, and dry mouth.[10] Similarly, the authors of this paper completed a mixed-methods study of head and neck cancer patients; they employed open interviewing as well as a modified Delphi technique. The findings mirrored the results published by Rogers et al., with the domains of swallowing, speech, chewing, and dry mouth identified as the most important.[10(p3)] In our search of the head and neck cancer literature, we found only two PRO instruments that measured at least one functional domain of swallowing, speech, chewing, or dry mouth and which also used head and neck cancer patients during their developmental process.

The first instrument we identified was the Swallowing Outcome after Laryngectomy (SOAL) questionnaire.[7] The SOAL instrument is well developed and demonstrates reliability, content, and construct validity. An evident limitation of the SOAL

questionnaire is that it is specifically intended for the subset of head and neck cancer patients who undergo laryngectomy. Therefore, this instrument would not necessarily be applicable for a large percentage of the head and neck cancer patient community whose primary tumor site is extra-laryngeal.

The second instrument we identified was the Xerostomia Questionnaire (XQ).[8] This instrument is intended for head and neck cancer patients receiving radiation. In their study, Eisbruch et al. demonstrated that the XQ is reliable with statistically proven construct validity. However, the limitations of the XQ surround its use of patients during its development. While the authors stated that patients were surveyed, no details of this interaction are given nor how these data were interpreted. Furthermore, once the XQ was developed, there was no formal cognitive assessment done of patients' understanding of the instrument's questions. The lack of formalized patient input during the development of the XQ has posed significant limitations to the content validity of this instrument.

In the speech domain, one of the most specific and widely used tools we encountered was the Speech Handicap Index (SHI).[11] The SHI was modified from the previously established Voice Handicap Index (VHI) and employs a 30-item Likert questionnaire. The SHI has been validated in an initial pilot study. However, as no patients were used in its inception, the SHI does not represent a true patient-centred outcome for head and neck oncology patients.[11]

In terms of chewing and jaw function, several PRO instruments exist in the literature, including the Jaw Functional Limitation Scale, the Research Diagnostic Criteria for Temporomandibular Disorders, and the Mandibular Functional Impairment

Questionnaire. These all employed patients during their development, but none of them used head and neck oncology patients.[12-14]

There are some limitations to our systematic review that may have resulted in missed relevant articles. Our inclusion criteria specified studies involving head and neck cancer patients with a diagnosis of squamous cell carcinoma. Studies that incorporated patients with other malignant diagnosis were excluded, despite if they also included squamous cell carcinoma patients. Relevant non-English studies were not included. Studies published after June 22, 2016, were not reviewed, and relevant studies may have been published during this time. It is also possible that relevant studies were missed due to human error.

3.5 CONCLUSION

The field of head and neck cancer surgery has made significant advancements in PROs over the last decade. Several PROs exist in the specialty. However, a large deficit of PROs that have employed head and neck patients during their development currently exists. Specifically, no such PROs exist for speech and chewing. Further research needs to be made in these areas to further propagate appropriate assessment of functional outcomes in head and neck cancer surgery.

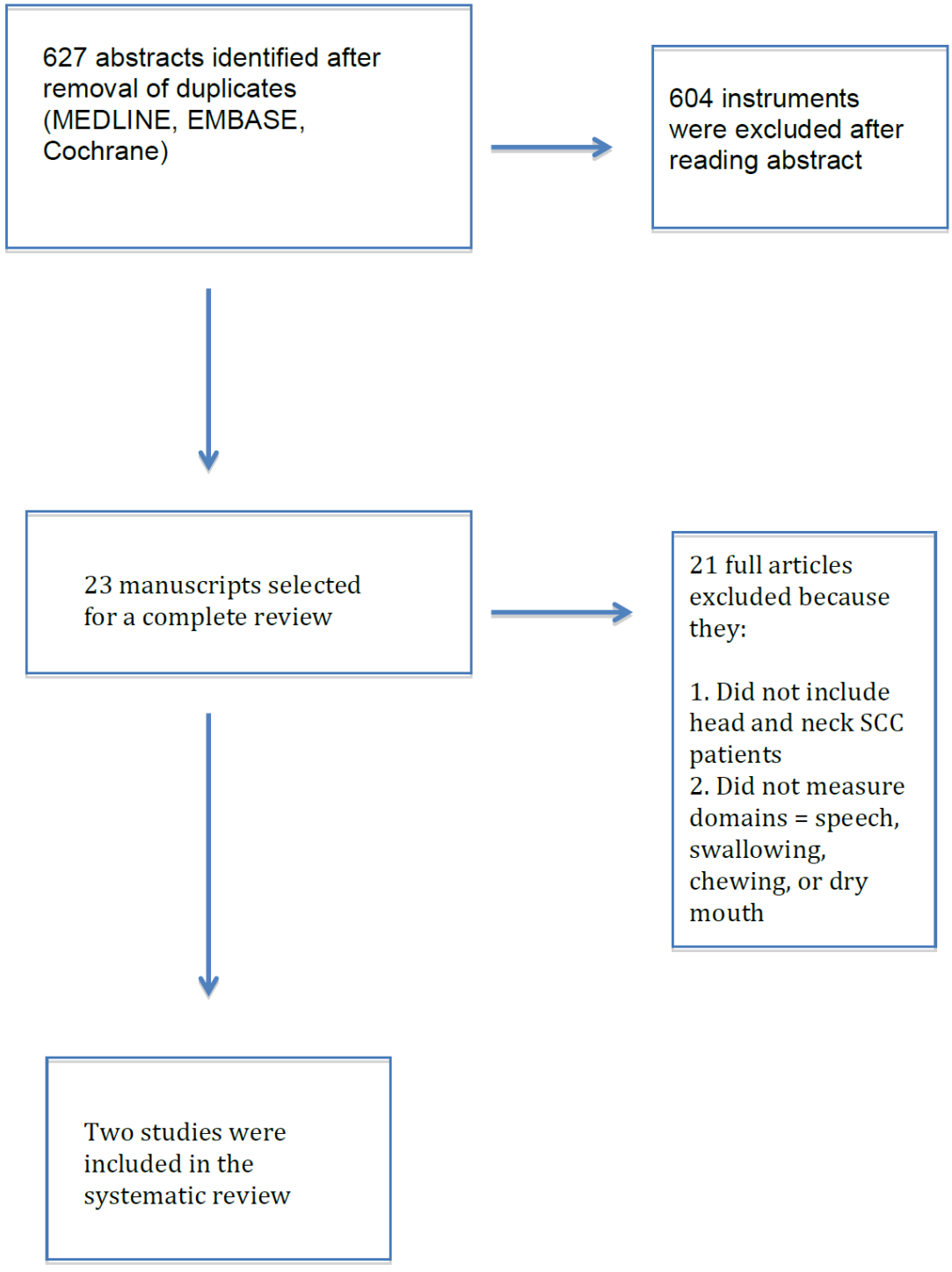
Table 3-1: Characteristics of Instruments Meeting Inclusion Criteria

Authors	Year(s) of Instrument Publication	Instrument Name	Intended Population	Domains Measured	Type of Response	Number of items
Eisbruch et al.	2001	Xerostomia Questionnaire (XQ)	Head and neck cancer patients receiving radiation (no specific tumor diagnosis given)	Xerostomia function	Rating scale	8
Govender et al.	2012	Swallow Outcomes After Laryngectomy (SOAL)	Patients having undergone laryngectomy (no specific diagnosis given, although implied to be head and neck cancer patients)	Swallowing function	Likert scale	17

Table 3-2: Reliability and Validity Statistics of Instruments Meeting Inclusion Criteria

Authors	Reliability	Content Validity	Construct Validity	Ability to Detect Change
Eisbruch et al.	*Internal consistency:* Cronbach's alpha = (0.86 pre-RT, 0.90 post-RT) *Test-retest:* Pearson's correlation coefficient r = 0.82 (p < 0.01)	Obtain head and neck cancer patient input? – YES Experts/literature review? – YES Cognitive interviewing? – NO	*Known-groups validity:* Unilateral vs. bilateral neck radiation groups (significantly different XQ scores from 1 to 24 months) *Criterion-validity:* XQ scores correlated with the dichotomous xerostomia instrument summary (r = 0.73, p < 0.01) baseline (r = 0.84, p < 0.01) 1 month post-RT	Baseline vs one month post-radiation in same patient population (significantly different XQ scores, p = 0.01)
Govender et al.	*Internal consistency:* Cronbach's alpha = 0.91	Obtain head and neck cancer patient input? – YES Experts/literature review? – YES Cognitive interviewing? - YES	*Known-groups validity:* Normal, laryngectomy, radiotherapy groups (significantly different SOAL scores, Mann-Whitney, p < 0.005) *Criterion-validity:* SOAL score correlated with MBS checklist score (r = 0.50, p = 0.03)	Not analyzed

Figure 3-1: Summary of study identification and exclusion process.



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CHAPTER 4: FUNCTIONAL DOMAINS OF IMPORTANCE TO THE HEAD AND NECK CANCER PATIENT: PHASES I AND II

4.1 INTRODUCTION

Shared decision making between patients and physicians has been widely endorsed as a model for making complex medical decisions, as it may have advantages including improved health outcomes and patient satisfaction. [1] Physicians and health care workers have expert knowledge regarding disease pathology, treatment options, and medical outcomes. However, patients are experts in their own preferences and desired outcomes.

Traditional treatment outcomes include objective measures such as serologic end points and diagnostic imaging, amongst others. It is now believed that these conventional outcomes do not provide all the information needed to understand treatment effects, as these outcomes do not incorporate the patient perspective.[2]

Over the past few decades, several disciplines of medicine have worked towards incorporating the patient perspective in outcomes research. In rheumatology, this led to the incorporation of fatigue and disturbed sleep in outcome measures, which are two domains that previously had not been evaluated.[3] Recently, the discipline of head and neck surgery has begun to attempt to incorporate patient perspectives in outcomes research. In order to build content validity, patient input is ideally procured through interviews and focus groups, where open-ended questioning can be implemented. This format creates the ability to capture unobservable patient experiences, including thoughts, feelings, and past experiences.[4] The purpose of this study was to specifically identify the functional domains of importance to the head and neck oncology patient. This

information will then be used in a future study to develop the first single patient-reported measurement scale for function in head and neck surgery.

4.2 MATERIALS AND METHODS

The larger institutions involved in patient-centred outcomes research (PCOR) are Outcome Measures in Rheumatology (OMERACT), Patient-Centered Outcomes Research Institute (PCORI), the US Food and Drug Administration (FDA) and the Patient Reported Outcomes Measurement Information System (PROMIS). A literature search was initially conducted of these institutions and their publications for guidance on methodology procedure. In 2011, the OMERACT group published an article detailing the process of domain selection.[5] The authors described a protocol similar to that outlined by the US FDA. The FDA process of domain selection is concisely illustrated in Figure 4-1, which is taken from their guidance report published in 2009 and involves engaging patients directly through interviewing.[6] In their 2011 article, OMERACT used four different case examples of how they completed domain selection within the framework of the US FDA protocol. The methodology our research group followed was based on both institutions and followed a two-phase design.[7,8]

4.2.1 Phase I and II design: Domain identification

This study was a mixed-methods study. Phase I identified the overall domains and functional outcome categories through patient qualitative interviewing and grounded theory.[9] Employing a focus group, Phase II refined the domain categories into a condensed list through a modified Delphi technique.[10]

Ethics approval was attained for this study in Canada from the University of Alberta Research Ethics Board (REB, reference number Pro00046886_AME3).

4.2.2 Phase I and II patient selection

Patients were recruited from the Head and Neck Cancer Clinic at the University of Alberta, Edmonton, Canada. The Head and Neck Cancer Clinic incorporates all facets of head and neck treatment, reconstruction, and rehabilitation for cancers and other head and neck disorders (e.g., thyroid). The clinic serves a source population of approximately four million people in central and Northern Alberta. Socio-demographic information was collected from each patient as well as tumor sub-site, tumor stage, treatment date, and treatment modality. The inclusion criteria followed included (1) age greater or equal to 18, (2) patients with a diagnosis of squamous cell carcinoma involving the sub-sites of the head and neck (i.e., oral cavity, oropharynx, hypopharynx, larynx), and (3) at least one year since definitive treatment. Any patients undergoing additional active medical treatment or with evidence of disease recurrence were excluded.

4.2.3 Phase I protocol

In order to limit selection bias, 10 patients meeting the inclusion and exclusion criteria outlined in Section 4.2.2 were selected from a single surgeon's clinic in chronological order of presentation. Data analysis was completed incrementally as each patient was enrolled in the study. Recruitment was terminated after 10 patients were chosen for Phase I, as no new domain categories were identified after the first six patients. Once patients were consented for the study, they then underwent a short interview designed to identify functional domains of interest. Patients were presented with the following four questions:

1. Tell me about your health…
2. What is important in terms of your health?
3. Other than survival, what is the most important thing treatment could do for you?
4. If you could improve one thing about your health, what would it be?

The above questions were generated from a literature search on functional outcomes in head and neck cancer as well as from grounded theory methodology. If patients required clarification regarding the questions, a scripted clarification paragraph was read to them. All patient interviews were audio recorded and transcribed verbatim.

4.2.4 Phase I: Grounded theory and data extraction

Analysis was performed by Adrian Mendez using the principles of grounded theory. Data analysis was further supported by the use of NViVo 7 software.[1] Transcribed interviews were then analyzed for descriptions of function. Inductive thematic analysis was used to extract small units of meaning, which were then given codes or labels (Figure 4-2).[9] Similar codes were then grouped together to form larger, overall categories (i.e., domains). To support the methodology being used during thematic analysis, two transcribed interviews were chosen at random and were independently analyzed by Hadi Seikaly. Codes between Hadi Seikaly and Adrian Mendez were compared for similarities.

4.2.5 Phase II protocol

An additional five patients meeting the inclusion and exclusion criteria were identified and selected to participate in *Phase II* of the study. Patients were excluded if they had already participated in *Phase I* of the study. Patients were selected from a single

surgeon's practice and were identified for having a high level of education, aptitude, and communication skills, as these characteristics lend themselves to favourable performance in small group settings. Patients also were chosen based on their tumor subsite. This helped ensure a wider range of the head and neck cancer spectrum experience was collected. Once patients were identified, they were contacted by phone and consented to the study. After being consented, patients were emailed and sent the domain result list from Phase I.

Patients were instructed to review the domain list and prioritize, in their opinion, from the most important domain to the least important. Patients were instructed to print a copy of the domain list and numerically rank domains. They were also asked to consider whether they personally felt a domain category was missing and, if so, to include this new domain in their rank list. Patients were instructed to bring this list to the focus group.

In order to reduce the large number of domain categories from Phase I to a top priority list, we implemented the modified Delphi technique. The Delphi technique is described as "a method for structuring a groups' communication process so that the process is effective in allowing a group of individuals as a whole, to deal with a complex problem."[12(p3)] The Delphi technique requires an expert panel, which can consist of individuals in a privileged, *expert position*, to individuals with international leadership in the questioned area. In our study, this expert panel consisted of patients with head and neck cancer, as these individuals were in unique positions to comment on importance in functional outcomes.

During the focus group, participants were first asked to share their previously formulated domain-ranking list. These results were then tabulated and presented back to the group on a large billboard. The group was then asked to engage in open discussion and debate and subsequently present a new domain ranking. Results were again tabulated. This process continued until greater than 70% consensus was achieved or no change ensued from round to round (Figure 4-3).

Once a top priority domain list was agreed upon, participants were then asked to begin formulating Likert-type statements that they felt would target the top priority domains they had identified. These would then be used in the generation of the itemized measurement tool in a future study.

4.3 RESULTS

In total, 10 head and neck oncology patients were included in Phase I of the study (Table 4-1). Patients' ages ranged from 37 to 76, and 60% were male. All four primary subsites of the head and neck were represented by the 10 patients. All Phase I interviews were conducted by AM at the Otolaryngology-Head and Neck Surgery clinic at the University Hospital in Edmonton, Canada. Overall, 25 initial themes were identified from the recorded transcripts. These initial themes were then grouped together into larger domains based on overlapping concepts. These larger domains were then grouped into functional domains and non-functional domains. The top domains of function identified in Phase I included speech, swallowing, chewing, dry mouth, pain, appearance, shoulder mobility, walking, and breathing (Table 4-2).

Five patients participated in Phase II (Table 4-3). Patients' ages ranged from 48 to 61, and 60% were male. The modified Delphi technique was employed during a two-hour focus group. Consensus during the modified Delphi technique was achieved over two rounds. The top four ranked functional domains identified after Phase II were swallowing, speech, dry mouth, and chewing (Table 4-4). The focus group additionally identified the need for social support for head and neck oncology patients before, during, and after treatment.

4.4 DISCUSSION

Recently, there has been an emphasis to standardize reported outcomes in medical disciplines.[13-15] Rheumatology has successfully created a *core set* of eight outcomes as an international standard in rheumatoid arthritis clinical trials. [16] Having standard reported outcomes in clinical research allows for direct comparison of treatments within and between different institutions. A valid core set is generally believed to require input from clinical experts (e.g., clinicians, researchers, etc.) as well as those individuals afflicted by the disease process in question (i.e., patients).[17] There have been several studies incorporating the clinician perspective in head and neck oncology.[15] Prinsen et al. recently initiated the COMET initiative, a large scale trial tasked with attaining expert clinician input in head and neck oncologic outcomes.[13] However, limited published research has attempted to identify patient concerns in head and neck oncology.

The purpose of this study was to identify the main functional domains of concern to the head and neck oncology patient. Our findings after Phases I and II (Table 4-4) correlated with those previously published in the literature. Rogers et al. followed over 1,500 head

and neck cancer patients for 10 years and administered a modified University of Washington Quality of Life scale at various time points. The authors found that throughout this time, four domains remained important to patients: swallowing, chewing, speech, and saliva.[18] Similarly, our study identified speech, swallowing, chewing, and dry mouth as the most important functional domains to head and neck cancer patients.

A potential limitation of this study is the small number of patients used in Phase I. Only 10 patients were included in Phase I because domain saturation was reached after six patients. However, numerous studies have conducted patient interviewing and found saturation with as few as five patient inteviews.[19,20]

A secondary objective of this study was to use the results from Phases I and II in a future Phase III study to create the first validated PRO for function in head and neck oncologic patients. Previous studies have identified 40 items or less as the ideal length of a PRO questionnaire. According to Krosnick and Presser, measurement instruments longer than 40 items become less valid, as respondents experience mental fatigue at these longer lengths.[21] In this study, the authors purposefully attempted to identify the top four functional domains of concern to the head and neck oncology patient in order to create a PRO of appropriate length.

4.5 CONCLUSION

In conclusion, this study was the first to identify functional areas of concern to the head and neck oncology patient using open-ended questioning and a modified Delphi technique. Patients with squamous cell carcinoma of the head and neck identified swallowing, speech, chewing, and dry mouth as the most important functional domains of

concern. These identified functional categories should be accounted for in creating a core outcome set in head and neck oncology.

Table 4-1: Phase I Patient Demographics

Category	Numerical Value
Total participants	*N* = 10
Average age	59.6 years
Sex	6 male, 4 female
Primary tumor site	4 oral, 3 larynx, 2 oropharynx, 1 hypopharynx

Table 4-2: Functional Domains Identified in Phase I

Domain Category	Domain
Function	Swallowing
Function	Speech
Function	Dry mouth
Function	Chewing
Non-Function	Pain
Non-Function	Appearance
Function	Shoulder mobility
Function	Walking
Function	Breathing

Table 4-3: Phase II Patient Demographics

Category	Numerical Value
Total participants	*N* = 5
Average age	55.2 years
Sex	3 male, 2 female
Primary tumor site	2 oral cavity, 1 larynx, 2 oropharynx

Table 4-4: Top Functional Domains Identified in Phase II

Domain	Rank
Swallowing	1
Speech	2
Dry mouth	3
Chewing	4

Figure 4-1: FDA process of patient-reported outcome (PRO) design.

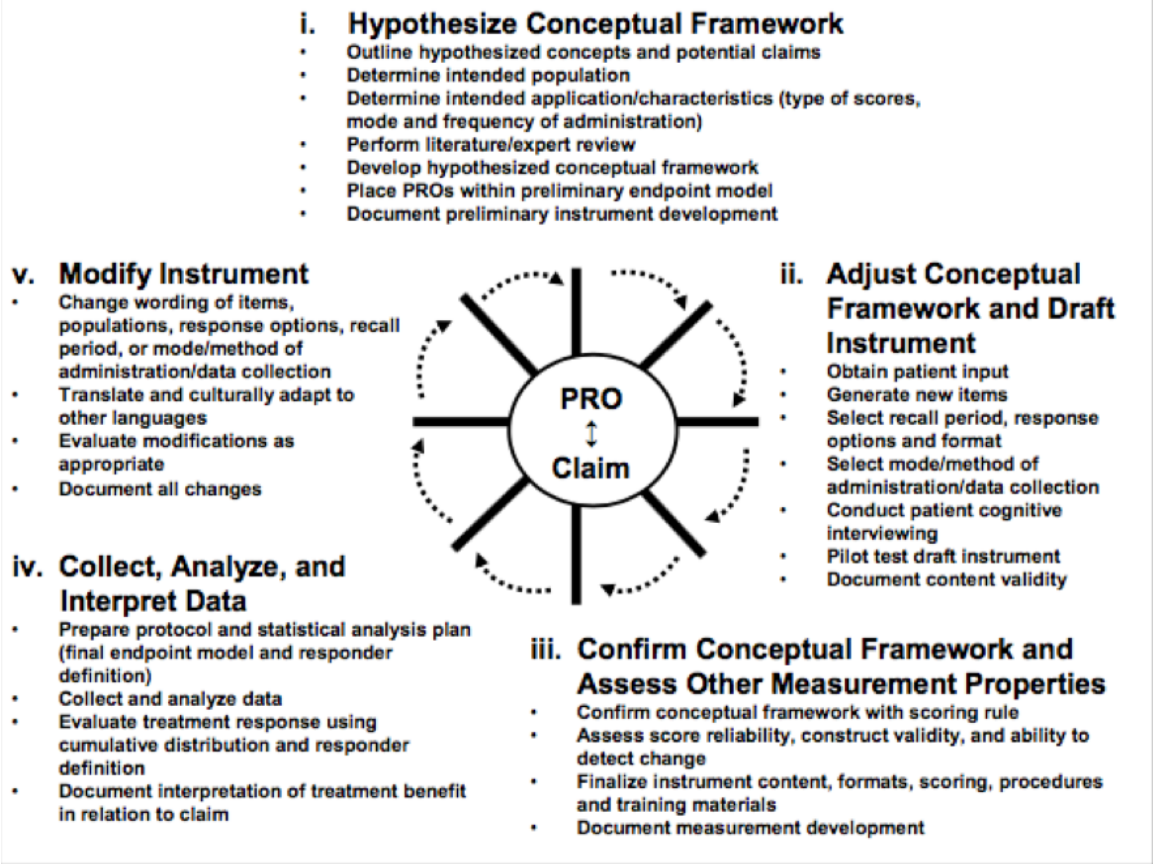


Figure 4-2: Phase I grounded theory methodology for functional domain identification.

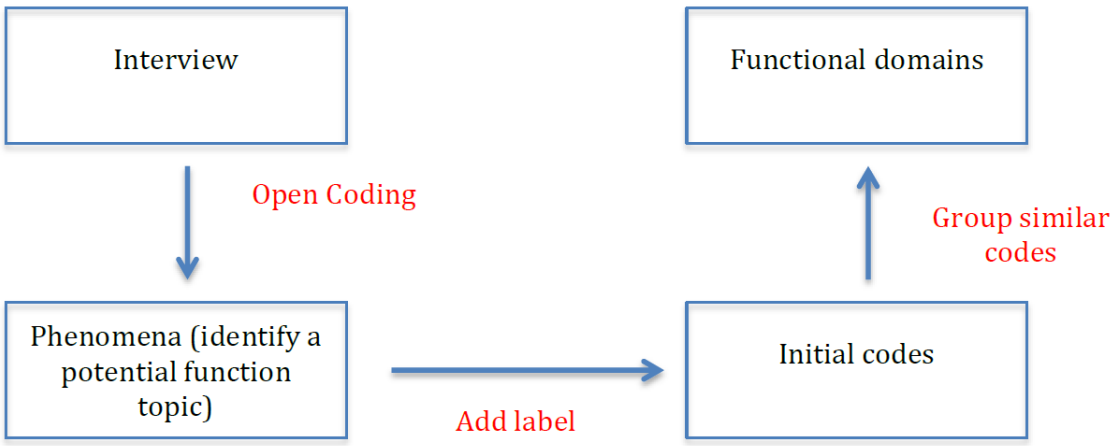
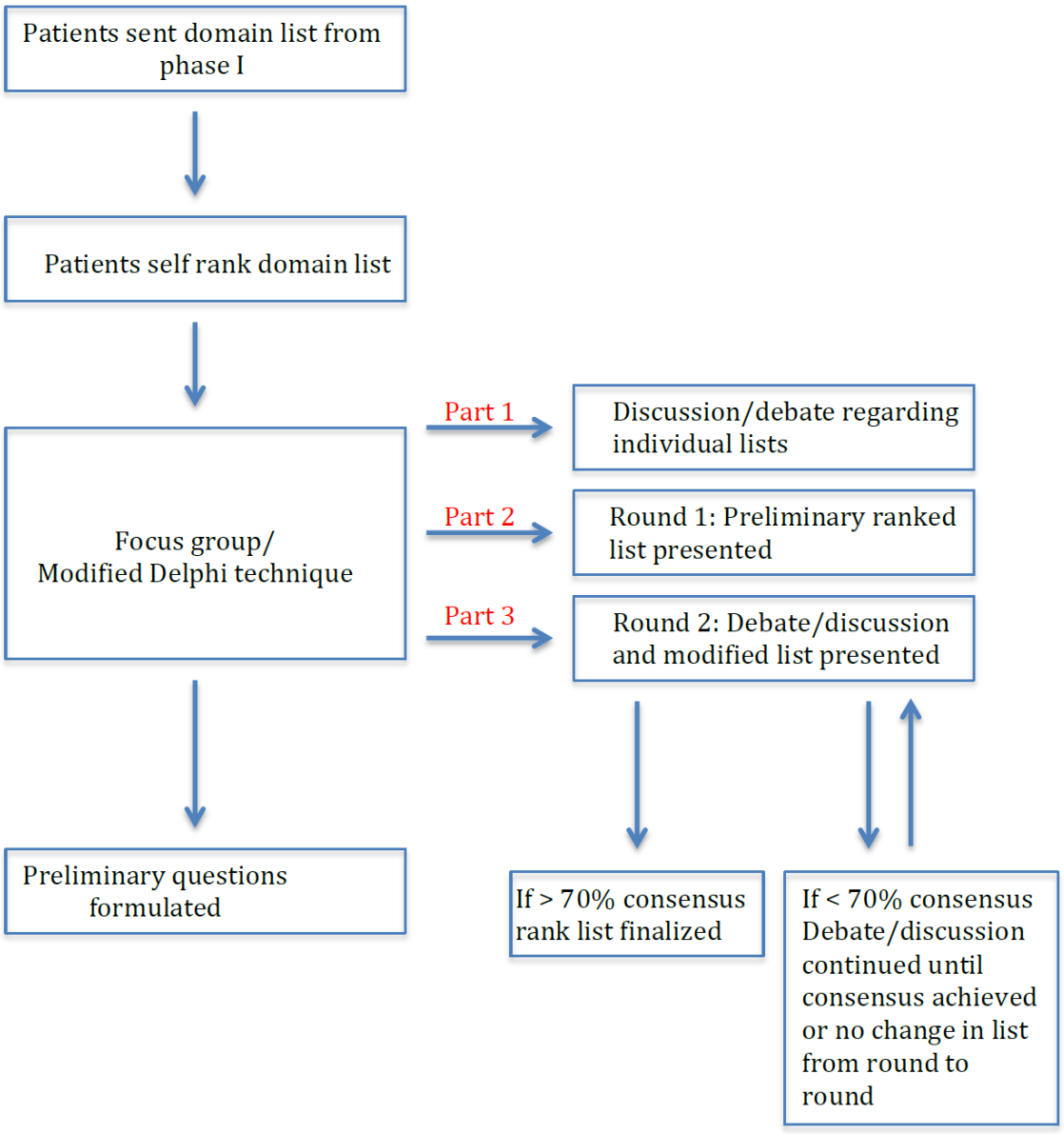


Figure 4-3: Methodological process of Phase II.



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CHAPTER 5: THE DEVELOPMENT OF THE HEAD AND NECK RESEARCH NETWORK-33: PHASE III

5.1 INTRODUCTION

5.1.1 Patient-centred outcomes research

In the field of clinical medicine, treatments are compared to one another by evaluating their effect using a set of pre-determined *outcomes*. The study of treatment comparison, in terms of benefits and harms, is known as comparative effectiveness research (CER).[1] Historically, clinicians and researchers as expert stakeholders determined these measured outcomes. However, it is now believed that these conventionally established outcomes do not fully express all the information needed to understand treatment effects on patients.[1]

As such, there has been a shift towards incorporation of patient perspectives in the outcomes literature.[2] Modern health care is patient-centric, where patients and their families are encouraged to actively participate in decision making. A comprehensive treatment evaluation is now believed to include patients' perspectives of treatments in terms of the patients' actual experiences in perceived functional impact.[1] This shift in the medical community's attitude towards patient involvement in health care decision making has led to the further development of the scientific field known as patient-centred outcomes research (PCOR). In its most basic definition,

> [PCOR] is research that is informed by the perspectives, interests, and values of patients throughout the research process, from the selection of research questions to the dissemination of research results. PCOR is intended to be practically relevant. Its real-world impact on patients is known and included in decisions about prevention, diagnosis and treatment.[3(p1)]

A natural extension of PCOR is the idea of a patient-reported outcome (PRO). Many important outcome measures are not easily assessed objectively, including outcomes such as chewing and pain. When attempting to measure subjective outcomes, these are best reported by patients themselves and are formally known as PROs. Furthermore, there exists "some outcomes that cannot reliably and accurately be assessed by any means other than direct patient report, so inclusion of PROs is often essential to patient-centeredness." [4(p28)] Although the previous statement can be applied to many disciplines of medicine, it holds special importance in head and neck oncology, as the majority of reported functional outcomes, such as taste and mastication, are patient specific.

5.1.2 Head and neck oncology and patient-centred outcomes research

The global impact of head and neck cancer on function is profound and often results in adverse quality of life outcomes.[5] Along with survival, functional outcomes are of high priority to cancer patients and are relevant when considering treatment strategies. [6] Assessment of functional outcomes in head and neck oncology is multidimensional, with broad subjective domains including fatigue, weakness, and difficulty with walking among others.[5] PROs can translate these patient experiences to measureable outcome scales, in a more accurate manner than conventional assessment tools. Furthermore, as functional outcomes are important parameters in head and neck cancer research, using PROs would allow for more standardized, accurate outcome assessment of head and neck treatments in the literature. PROs additionally have the advantage of being accessible to all health care professionals, allowing this type of outcome measurement the ability to be universal.

Although it would appear there are an abundance of questionnaires and PROs used in the field of head and neck cancer surgery, almost all of these lack a crucial developmental

process—inclusion of patients in their inception. Multiple organizations specializing in patient-centred outcome research (PCORI, FDA, PROMIS, and OMERACT) underline the importance of including the specific patient population, which was tested in the actual development of the PRO.[7-9] Given this gap in head and neck oncology outcome research, the objective of this study was to create and validate the first instrument to measure the main functional areas of concern of the head and neck oncology patient.

5.2 METHODS

Essential to meeting the objective of creating a single measurement tool to assess the main functional outcomes of interest to head and neck cancer patients, identification of the most important outcomes (i.e., domains) to the patients was a critical first step. Evidently, this would entail engaging the patients, as they were the only accurate source of this information.

The larger institutions involved in patient-centred outcome research (PCOR) are the Outcome Measures in Rheumatology (OMERACT), Patient-Centered Outcome Research Institute (PCORI), the US Food and Drug Administration (FDA), and the Patient Reported Outcomes Measurement Information System (PROMIS). A literature search was initially conducted of these institutions and their publications for guidance on methodology in creating a PRO. In 2011, the OMERACT group published an article detailing the process of domain selection.[10] The authors described following a protocol similar to that outlined by the FDA. The FDA process of domain selection is concisely illustrated in Figure 5-1, which has been taken from their guidance report published in 2009. [9] In their 2011 article, the OMERACT group described how they completed

domain selection within the framework of the FDA protocol. The methodology our research group followed was based on both institutions and followed a four-phase design.[11,12]

5.2.1 Phases I and II: Domain identification

This study is a mixed methods study. Phase I identified the overall domains and functional outcome categories through patient qualitative interviewing and grounded theory. [13] Phase II refined the domain categories into a condensed list through a modified Delphi technique, employing a focus group.[14]

Ethics approval was attained for this study from the University of Alberta Research Ethics Board (REB, reference number Pro00046886_AME3).

5.2.2 Phases I and II: Patient selection

Patients were recruited from the Head and Neck Cancer Clinic at the University of Alberta. Socio-demographic information was collected from each patient as well as tumor sub-site, tumor stage, treatment date, and treatment modality. The inclusion criteria included (1) age greater or equal to 18, (2) patients with a diagnosis of squamous cell carcinoma involving the sub-sites of the head and neck (i.e., oral cavity, oropharynx, hypopharynx, larynx), and (3) at least one year since definitive treatment. Any patients undergoing additional active medical treatment or with evidence of disease recurrence were excluded.

5.2.3 Phase III: Item generation

The primary objective of Phase III of the study was to develop the initial itemized questionnaire that would target the top prioritized domains identified in Phases I and II of

the study. An ideal itemized questionnaire included information collected from patients, the literature, as well as input from a group of expert stakeholders.[9] In this study, the patient input generated in Phases I and II was used to represent the patient contribution in Phase III.

Prior to undertaking this study, the authors completed a systematic review of PROs that currently exist in the head and neck literature. From this systematic review, we identified itemized instruments that had already been published that specifically targeted the prioritized domains identified in Phases I and II. Expert stakeholders in head and neck oncology include surgeons, clinicians, researchers, as well as speech language pathologists. We identified a group that included three surgeons, two clinicians, two researchers, and one speech language pathologist.

5.2.4 Phase III Protocol

In order to arrive at a condensed itemized list that included input from all three groups (i.e., patients, literature, expert stakeholders), we again implemented a modified Delphi technique. This process involved the expert stakeholder group equipped with the patient- and literature-derived information.

Each member of the expert stakeholder group was sent a list of the most important PROs currently found in the literature of each of the domains identified in Phases I and II. Furthermore, they were sent a list of the generated items created by the patients in Phase II. They were asked to review this information in preparation for a subsequent focus group that they would be participating in.

During the focus group, participants were first asked to share the items they felt were the best from those they had received. These results were then tabulated and presented back to the group on a large digital screen. The group was then asked to engage in open discussion and debate regarding each individual item to decide whether it should be kept, discarded, or modified. Results were again tabulated. This process continued until consensus was achieved or no change ensued from round to round (Figure 5-2). Finally, the group was asked to add any addition items they felt were important but not yet represented.

Once this initial itemized list was created, this was given back to a new group of 10 head and neck oncology patients. They were asked to complete the itemized questionnaire out loud (i.e., cognitive interviewing) in order to ensure comprehension (Figure 5-2). Any further modifications to question wording were then made for comprehension purposes.

5.3 RESULTS

In total, 10 head and neck oncology patients were included in Phase I of the study (Table 5-1). The domains of function identified in Phase I included speech, swallowing, chewing, dry mouth, pain, and appearance (Table 5-2).

Following the modified Delphi technique of Phase II, the top four ranked functional domains identified were swallowing, speech, dry mouth, and chewing, listed in order of priority (Table 5-3 and Table 5-4).

The final instrument developed was a 33-item, Likert-type scale containing the domains of swallowing, speech, xerostomia, and chewing (Appendix 5-1). Entitled the Head and

Neck Research Network-33 (HNRN-33), 11 items addressed swallowing function, 10 items addressed speech, while seven items pertained to xerostomia and five items to chewing. All items were scored 1 through 5 with verbal descriptors (e.g., strongly agree, agree, etc.) used as possible answers. In addition, respondents could also choose N/A (i.e., not applicable), in which case that item would be removed from the overall scoring. Each domain had possible scores from 0 to 100. For each domain, a linear transformation was completed as follows to attain a score between 0 and 100:

If items $I_1 + I_2 + I_3 + \ldots + I_n$ are included in the scale, the calculation is as follows:

$$\text{Raw Score} = RS = (I_1 + I_2 + I_3 + \ldots + \underline{I_n})/n$$

$$\text{Domain Score} = \{(RS - 1)/\text{question score range}\} \times 100$$

A score of 100 indicated high function, while a score of 0 indicated relatively poor function in the scored domain.

5.4 DISCUSSION

The idea of comparative medicine has been implemented for several decades, primarily by the pharmaceutical industry and private sector.[15] The concept of comparative medicine has also gained traction in many areas of medicine, as clinicians and researchers search for the best evidence-based therapeutic option to treat their patients. Particularly in the field of head and neck oncology, where debate remains regarding whether primary surgery or radiation offers the best outcomes, researchers have been publishing treatment outcome studies for several years.[16-18] These studies have led to the development of a multitude of outcome instruments in the head and neck oncology literature.

In their methodology document published in 2012, PCORI stated that as a minimum standard, patients of interest need to be included in the development of PROs.[8] Furthermore, Kirwan et al., from the Outcome Measure in Rheumatology (OMERACT) group, stated that data from questionnaires are invalid if the instruments do not include patients in their development.[7] Prior to the commencement of this study, the authors performed a systematic review of the literature for PROs currently in existence in the head and neck oncology literature. Our systematic review of the English-language literature identified 213 abstracts flagged for full article review. Eight potential instruments were identified within the domains of speech (n = 1), swallowing (n = 3), chewing (n = 3), and dry mouth (n = 1). However, only two of these instruments, both within the domain of swallowing, satisfied the minimal requirement of including head and neck cancer patients in its development, leaving a significant deficit in the literature. Specifically, no single PRO exists in the head and neck literature to assess the most important areas of function.

The choice of *what* functional outcome to assess and *how* to assess it is extensive. This creates significant difficulty with comparing treatment modalities for head and neck cancer, as different research centres choose to report different outcomes. Recently, there has been an effort to standardize which outcome measures to report in head and neck cancer to allow efficient treatment comparisons universally. A widely used method to accomplish this task is identifying a core outcome set, which refers to outcomes that should be consistently measured and reported in clinical trials.[19]

The HNRN-33 includes the domains of swallowing, speech, dry mouth, and chewing, which are representative of a core outcome set for function in head and neck cancer, as

those domains were specifically prioritized by head and neck cancer patients. We limited the domain number to four, as this allowed the creation of an instrument of appropriate length to limit patient burden. We also chose to use a Likert-type scale in the HNRN-33, as there are some indications that verbal descriptors (i.e., strongly agree, agree, etc.) response options create more valid responses.[20] Furthermore, Likert-type scales are also commonly used in patient-reported outcome measures.

Our top four domain findings from Phases I and II were consistent with that previously published in the literature. In 2013, Rogers et al. published their study, which looked at what outcomes head and neck cancer patients considered important.[6] The authors noted that what patients prioritized varied depending on tumor site and progression of the disease. However, four outcomes remained consistent, and these included speech, swallowing, chewing, and dry mouth.[6]

5.5 CONCLUSION

The HNRN-33 is the first PRO instrument designed to assess functional outcomes in head and neck oncology patients and could serve as a single comprehensive measure for functional outcomes. The HNRN-33 instrument is presented in Appendix 5-1.

Table 5-1: Phase I Patient Demographics

Category	Numerical Value
Total participants	*N* = 10
Average age	59.6 years
Sex	6 male, 4 female
Primary tumor site	4 oral, 3 larynx, 2 oropharynx, 1 hypopharynx

Table 5-2: Functional Domains Identified in Phase I

Domain Category	Domain
Function	Swallowing
Function	Speech
Function	Dry mouth
Function	Chewing
Non-Function	Pain
Non-Function	Appearance
Function	Shoulder mobility
Function	Walking
Function	Breathing

Table 5-3: Phase III Patient Demographics

Category	Numerical Value
Total participants	*N* = 5
Average age	55.2 years
Sex	3 male, 2 female
Primary tumor site	2 oral cavity, 1 larynx, 2 oropharynx

Table 5-4: Top Functional Domains Identified in Phase II

Domain	Rank
Swallowing	1
Speech	2
Dry mouth	3
Chewing	4

Figure 5-1: FDA process of patient-reported outcome (PRO) design.

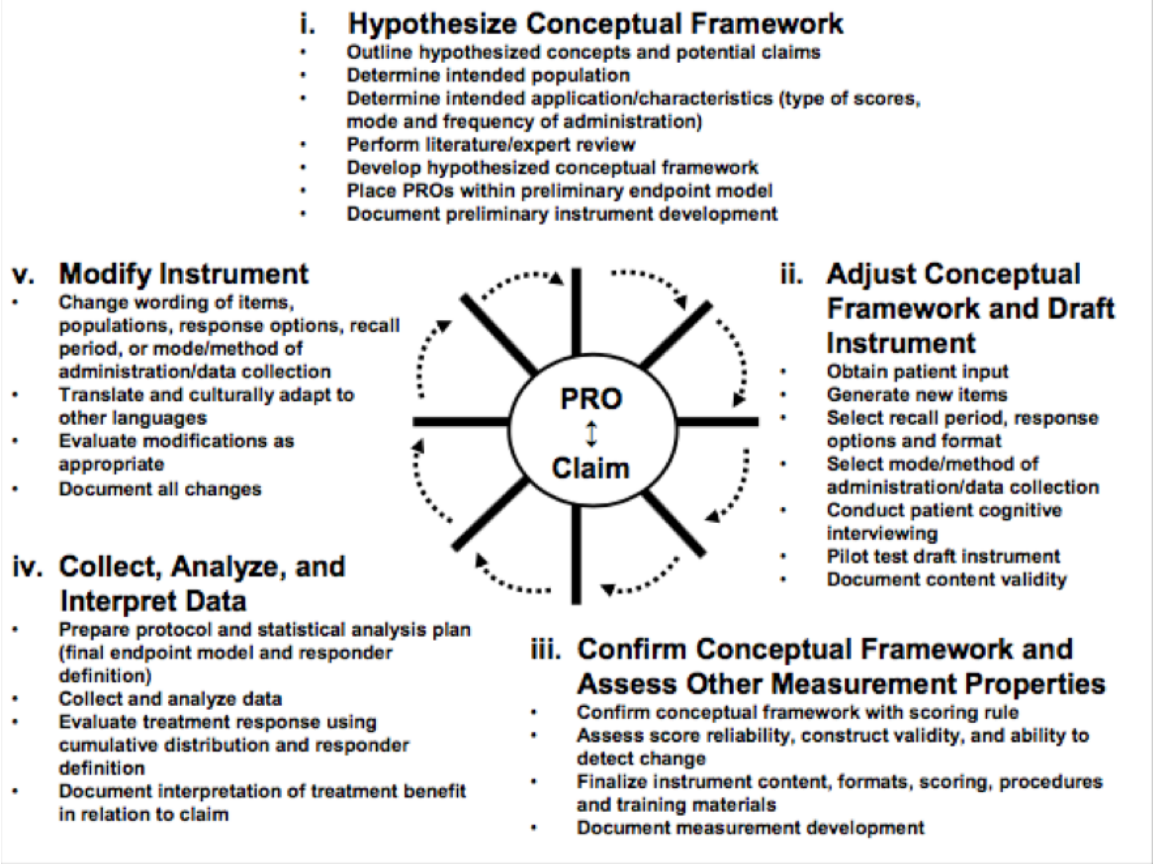
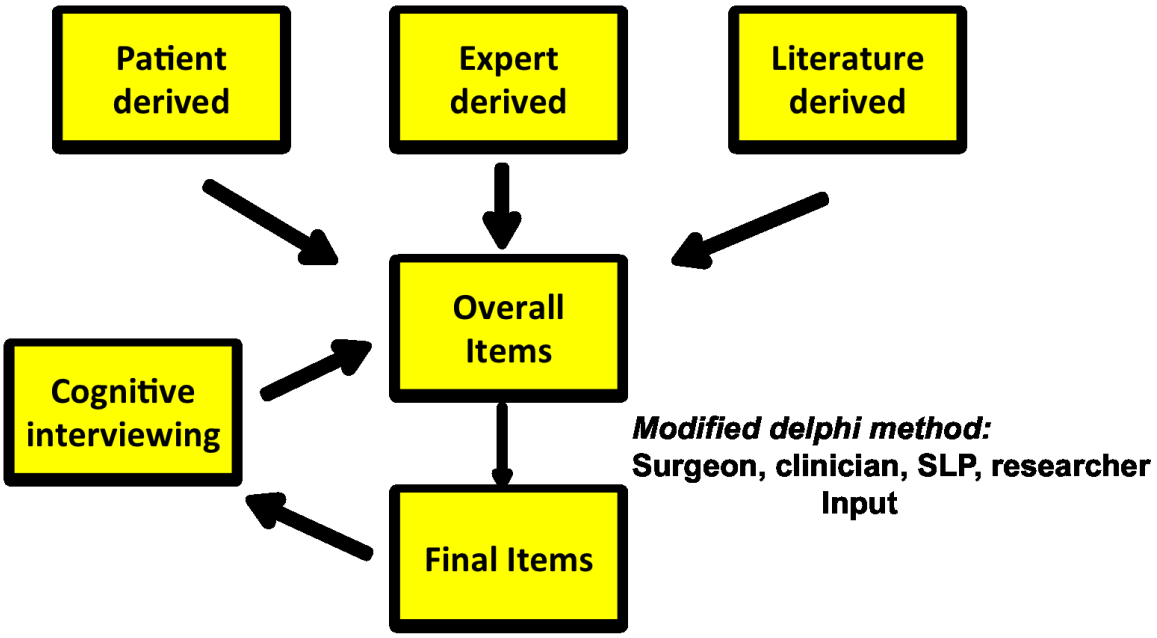


Figure 5-2: Methodological process of Phase III.



Appendix 5-1: The Head and Neck Research Network-33 (HNRN-33)

The HNRN-33 is a questionnaire to assess how well head and neck cancer patients are swallowing, speaking, chewing, and producing saliva. There are 33 items below. For each item, please select how strongly you agree with the statement from the options.

1. I can swallow normally

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

2. Swallowing takes great effort

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

3. It takes me longer to eat than others because of my swallowing problem

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

4. I cough or choke when I try to drink liquids

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

5. I limit my food intake because of my swallowing difficulty

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

6. I can maintain my weight by eating

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

7. Food or liquids dribble out of my mouth

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

8. Food or liquids comes out of my nose

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

9. I have to plan ahead about eating because of my swallowing

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

10. I avoid eating certain types of food because of my swallowing problem

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

11. I cough or choke when I eat solid food

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

12. I can speak normally

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

13. My speech sounds “nasal”

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

14. I avoid using the phone because of my speech problem

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

15. I find it difficult to pronounce certain words

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

16. My speech sounds slurred

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

17. People ask me to repeat myself when speaking face-to-face

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

18. It takes me longer to say something because of my speech problem

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

19. I use a lot of effort to speak

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

20. My voice makes it difficult for people to hear me

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

21. My voice sounds creaky and dry

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

22. My mouth feels dry

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

23. I have difficulty in eating dry foods because of my dry mouth

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

24. I must sip liquids to aid in swallowing foods because of my dry mouth

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

25. I use hard candy, gum or other products to relieve my dry mouth

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

26. I have thick “ropey” saliva

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

27. I carry liquids with me at all times because of my dry mouth

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

28. My mouth dryness makes it difficult to speak

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

29. I can chew normally

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

30. I have trouble chewing hard food because of my teeth, mouth, or dentures

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

31. It takes me longer to eat than others because of my chewing problem

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

32. I have trouble opening my mouth wide enough to eat

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

33. I have problems moving food around with my tongue

Strongly agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
5	4	3	2	1	0

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CHAPTER 6: THE VALIDATION OF THE HEAD AND NECK RESEARCH NETWORK-33: PHASE IV

6.1 INTRODUCTION

Patient-centred outcomes research is an evolving area of investigation in the head and neck oncology literature. Here, this topic is briefly introduced as well as its evolving role in head and neck oncology and the objective of this study.

6.1.1 Patient-centred outcomes research

In the field of clinical medicine, treatments are compared to one another by evaluating their effect using a set of pre-determined *outcomes*. The study of treatment comparison, in terms of benefits and harms, is known as comparative effectiveness research (CER).[1] Historically, clinicians and researchers as expert stakeholders determined these measured outcomes. However, it is now believed that these conventionally established outcomes do not fully express all the information needed to understand treatment effects on patients.[1]

A comprehensive treatment evaluation is now believed to include patients' perspectives of treatments in terms of the patients' actual experiences in perceived functional impact.[1] This shift in the medical community's attitude towards patient involvement in health care decision making has led to the further development of the scientific field known as patient-centered outcomes research (PCOR). A natural extension of PCOR is the idea of a patient-reported outcome (PRO). When attempting to measure subjective outcomes, these are best reported by patients themselves and are formally known as PROs.

6.1.2 Head and neck oncology and patient-centred outcomes research

Although it would appear there are an abundance of questionnaires and PROs used in the field of head and neck cancer surgery, almost all of these lack a crucial developmental process—inclusion of patients in their inception. Multiple organizations specializing in patient-centred outcome research (PCORI, FDA, PROMIS, and OMERACT) underline the importance of including the specific patient population, which was tested in the actual development of the PRO.[2-4] Given this gap in the head and neck oncology outcome research, the authors of this study have worked towards creating the first instrument to measure the main functional areas of concern of the head and neck oncology patient through a four-phase methodological process.

The authors previously identified and reported on the most important functional domains to the head and neck oncology patient, as reflected in Phases I and II. The results of that research study were then used to create the Head and Neck Research Network-33 (HNRN-33), the first single patient-reported measurement scale for functional domains of swallowing, speech, chewing, and dry mouth (Phase III). The objective of this study is to validate the Head and Neck Research Network-33 instrument (Phase IV).

6.2 METHODS

Essential to meeting the objective of creating a single measurement tool to assess the main functional outcomes of interest to head and neck cancer patients, identification of the most important outcomes (i.e., domains) to the patients was a critical first step. Inherently, this would require engaging the patients themselves as the source of this information.

The larger institutions involved in patient-centred outcome research (PCOR) are the Outcome Measures in Rheumatology (OMERACT), Patient-Centered Outcome Research Institute (PCORI), the US Food and Drug Administration (FDA), and the Patient Reported Outcomes Measurement Information System (PROMIS). A literature search was initially conducted of these institutions and their publications for guidance on methodology in creating a PRO. In 2011, the OMERACT group published an article detailing the process of domain selection.[5] The authors described following a protocol similar to that outlined by the FDA. The FDA process of domain selection is concisely illustrated in Figure 6-1 taken from their guidance report published in 2009.[4] In their 2011 article, the OMERACT group described how they completed domain selection within the framework of the FDA protocol. The methodology our research group followed was based on both institutions and followed a four-phase design.[6,7]

6.2.1 Phases I and II: Domain identification

Phases I and II were included together in a mixed-methods study. Phase I identified the overall domains and functional outcome categories through patient qualitative interviewing and grounded theory.[8] Phase II refined the domain categories into a condensed list through a modified Delphi technique, employing a focus group comprised with additional head and neck cancer patients.[9] The results of the first two phases were the identification of swallowing, speech, chewing, and dry mouth as the most important functional domains to the head and neck cancer patient. For further details regarding Phases I and II, please see Chapter 4.

6.2.2 Phase III: Item generation

The primary objective of Phase III was the development of an initial itemized questionnaire that would target the top prioritized domains to head and neck cancer patients, identified in the first two phases of the study. Information collected from three separate groups was used to create the questionnaire, which included patients, published relevant literature, as well as input from a group of expert stakeholders.[4] The result was the development of the Head and Neck Research Network-33 (HNRN-33). Further details regarding Phase III can be found in Chapter 5.

6.2.3 Phase IV: Validation

In order for any instrument to be valid, both content and construct validity must be demonstrated. Content validity is the estimate of how much a measure represents every single element of a construct. Content validity is qualitative in nature and is often demonstrated by thorough methodology. The HNRN-33 is purported to be an instrument that encapsulates the most important domains of function to head and neck oncology patients. Content validity of the HNRN-33 has already been demonstrated by the inclusion of head and neck oncology patients and their responses in the development of the instrument during Phases I and II.

This Phase IV validity study focused directly on the construct validity of the HNRN-33: that is, the degree to which the instrument is capable of measuring the functional domains of swallowing, speech, chewing, and dry mouth. To demonstrate construct validity, we performed criterion-validity (i.e., correlation) testing correlating HNRN-33 scores with previously validated objective and subjective instruments of function in head and neck

oncology. We also performed factor analysis of HNRN-33 responses consisting of a larger, multi-institutional head and neck cancer sample population.

Ethics approval was attained for this study in Canada from the University of Alberta Research Ethics Board (REB, reference number Pro00046886_AME3).

6.2.4 Phase IV: Criteria validity testing

Patients were recruited from the Head and Neck Cancer Clinic at the University of Alberta, Edmonton, Canada. Socio-demographic information was collected from each patient as well as tumor sub-site, tumor stage, treatment date, and treatment modality. The inclusion criteria included (1) age greater or equal to 18, (2) patients with a diagnosis of squamous cell carcinoma involving the sub-sites of the head and neck (i.e., oral cavity, oropharynx, hypopharynx, larynx), and (3) at least one year since completion of definitive treatment. Any patients undergoing additional active medical treatment or with evidence of disease recurrence were excluded.

Twenty-five patients meeting the inclusion and exclusion criteria were selected in chronological order to limit selection bias. Consented patients performed the HNRN-33 study instrument as well as completed testing designed to objectively and qualitatively measure swallowing, speech, chewing, and xerostomia. Objective testing included completing a modified barium swallow, g-tube use analysis, and speech intelligibility. Qualitative measurements included completing the MD Anderson Dysphagia Inventory (MDADI) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Head and Neck 35 (EORTC QLQ-H&N35). All testing was completed within two weeks for each individual patient. Following qualitative and

objective testing, statistical correlation between the HNRN-33 and each individual qualitative and objective testing measure was completed using Pearson's correlation coefficient.

6.2.5 Qualitative testing

The MD Anderson Dysphagia Inventory is a 20-item questionnaire to assess dysphagia, scored from 0 to 100, with 100 representing high function.[10] Questions pertain to three distinct aspects; emotional, functional, and physical. Five possible responses to the items on the MDADI were printed for each item, which included strongly agree, agree, no opinion, disagree, or strongly disagree.

The EORTC QLQ-H&N35 is meant for use among a wide range of patients with head and neck cancer, varying in disease stage and treatment modality. The head and neck cancer module incorporates seven multi-item scales that assess pain, swallowing, senses (i.e., taste and smell), speech, social eating, social contact, and sexuality. There are also 11 single items. For all items and scales, high scores indicate more dysfunction.[11]

6.2.6 Objective testing

The penetration-aspiration scale was used to assess swallowing function from modified barium swallow testing. The scale is an 8-point, equal-appearing interval scale to describe penetration and aspiration events. Scores are determined primarily by the depth to which material passes in the airway and by whether or not material entering the airway is expelled, with a score of 1 indicating no material entering the airway and a score of 8 indicating frank aspiration with no ejection effort.[11]

Perceptual assessment of speech was completed by collecting speech samples at both the word and the sentence level. Bead-mounted unidirectional microphones were used to digitally record speech intelligibility scores. Speech stimuli included 50 words and 22 sentences randomly generated by the Computerized Assessment of Intelligibility of Dysarthric Speech. Intelligibility scores were determined by a research assistant, blinded to the treatment modality, who listened to the patient's tape recordings and transcribed what he or she perceived the patient to have said. Listener transcriptions were compared with a key that was kept in the patient's file. Reanalysis of the speech sample by a second judge was used to establish inter-judge reliability.[12]

6.2.7 Factor analysis

Factor analysis uses mathematical procedures for the simplification of interrelated measures to discover patterns in a set of variables.[13] Factor analysis was performed with data from the HNRN-33 in order to confirm item grouping (e.g., swallowing, speech, etc.) as well as delineate redundancy within the questionnaire.

In order to accrue an appropriate sample size for statistical analysis, we completed a multi-institutional study involving the following subsites: (1) University Hospital, University of Alberta, Edmonton, Canada; (2) Mount Sinai Health Network, New York City, U.S.A.; (3) University of Turku, Turku, Finland. One hundred and one patients were recruited into the study and asked to complete the HNRN-33.

Patients were recruited from each of the three sites. Socio-demographic information was collected from each patient as well as tumor sub-site, tumor stage, treatment date, and

treatment modality. Inclusion and exclusion criteria used were as described in Section 6.2.4.

Consented patients were given a copy of the HNRN-33 and asked to complete the questionnaire. No time limit was administered, and no additional instructions were given in order to standardize the responses. Statistical analysis was performed using STATA after a sample size of at least 100 patients was achieved.

The HNRN-33 was adapted and translated into Finnish for use in the Turku subsite. The translation was completed by a Finish clinician, fluent in both Finish and English.

6.3 RESULTS

Overall, 25 head and neck oncology patients participated in the Phase IV validation component of this study, with their respective demographics outlined in Table 6-1. All recruited patients completed the HNRN-33 questionnaire as well as the MDADI and the EORTC QLQ-H&N35. Furthermore, all recruited patients completed a modified barium swallow and speech intelligibility testing.

6.3.1 Criteria validity and correlation studies

The mean domain scores of the 25 patients for swallowing, speech, dry mouth, and chewing recorded for the HNRN-33 were 66.5, 61.7, 59.1, and 54.1, respectively. The individual patient scores of the HNRN-33 were then compared using Pearson's correlation coefficient, *r*, to the other objective and qualitative testing the patients underwent.

When correlating the HNRN-33 swallowing domain scores with objective and qualitative assessments of swallowing, statistically significant correlation was observed (Table 6-2). A moderate to strong negative *r* correlation of -0.60 was observed between the HNRN-33 scores and the penetration-aspiration scale scores from the modified barium swallow. A strong positive correlation of 0.77 was observed between the HNRN-33 scores and the MDADI total scores (Figure 6-2). A strong negative correlation of -0.73 was observed between the HNRN-33 scores and the EORTC QLQ-H&N35 swallowing scores (Figure 6-3). All correlations were statistically significant ($p < 0.05$).

Similarly, when comparing HNRN-33 speech swallowing domain scores with objective and qualitative speech assessments, statistically significant linear correlations were observed (Table 6-2). Moderate to strong positive *r* correlations of 0.55 and 0.61 were observed between the HNRN-33 scores and sentence and word intelligibility, respectively. Furthermore, a moderate to strong negative *r* correlation of -0.64 was observed between HNRN-33 scores and Speech Handicap Index scores. All correlations were statistically significant.

The HNRN-33 dry mouth domain scores were compared to the EORTC QLQ-H&N35 dry mouth symptom scores for validation. A moderate to strong negative *r* correlation of -0.54 was observed between the two groups, with the correlation coefficient being strongly significant (Table 6-2).

In the final domain of chewing, the HNRN-33 scores had a weak to moderate negative correlation of -0.45 and -0.43 to the EORTC QLQ-H&N35 symptom scores of mouth

opening and trouble with social eating, respectively. These correlation coefficients were also both statistically significant (Table 6-2).

6.3.2 Factor analysis

Overall, 101 head and neck oncology patients completed the HNRN-33 for the purpose of factor analysis. Forty-nine of these patients were from the University of Alberta, in Edmonton, Alberta. Thirty-two patients were recruited from the Mount Sinai Health Center in New York City, NY, while 20 patients were recruited from the University of Turku in Turku, Finland (Table 6-3). Average patient response time to complete the HNRN-33 was 130 seconds.

All participants had a diagnosis of squamous cell carcinoma (SCC) of the head and neck. The average age of the participants was 64. Sixty percent of the patients had primary oral cavity SCC, while 20% had primary oropharyngeal SCC. The remaining 20% of the patients had either a diagnosis of primary laryngeal SCC or hypopharyngeal SCC (Table 6-3).

The results of the factor analysis for the HNRN-33 are summarized in Table 6-4. The factor loading values for the domains of swallowing, speech, dry mouth, and chewing are all greater than 0.3 with p-values < 0.001. The mean factor loading values for the items relating to swallowing and speech were 0.71 and 0.76, respectively. The mean factor loading values for the items relating to dry mouth and chewing were 0.71 and 0.77, respectively. These values represent very strong loading values between the individual items and their respective domains. Figures 6-4, 6-5, 6-6, and 6-7 illustrate the individual

item factor loading values for each domain and additionally compare the data when patients from the Turku site are not included in the data.

6.4 DISCUSSION

The choice of *what* functional outcome to assess and *how* to assess it is extensive. This creates significant difficulty with comparing treatment modalities for head and neck cancer, as different research centres choose to report different outcomes. Recently, there has been an effort to standardize which outcome measures to report in head and neck cancer to allow efficient treatment comparisons universally. A widely used method to accomplish this task is identifying a core outcome set, which refers to outcomes that should be consistently measured and reported in clinical trials.[14]

The HNRN-33 includes the domains of swallowing, speech, dry mouth, and chewing, which are representative of a core outcome set for function in head and neck cancer, as those domains were specifically prioritized by head and neck cancer patients themselves. We limited the domain number to four, as this allowed the creation of an instrument of appropriate length to limit patient burden. Our top four domain findings from Phases I and II were consistent with that previously published in the literature. In 2013, Rogers et al. published their study, which looked at what outcomes head and neck cancer patients considered important.[15] The authors noted that what patients considered important varied depending on tumor site and progression of the disease. However, four outcomes remained consistent, and these included speech, swallowing, chewing, and dry mouth.[15]

Our Phase IV validation study indicated that the HNRN-33 correlates well with commonly used and widely accepted qualitative instruments to measure swallowing,

speech, dry mouth, and chewing. Of note, the HNRN-33 also had moderate to strong correlation with objective assessments of swallowing and speech. Factor analysis calculations further confirmed that the items in the HNRN-33 cover four separate domains, with similarly grouped items loading onto one of swallowing, speech, chewing, or dry mouth domains (Figure 6-8). Factor analysis also confirmed that no individual item from the 33 was redundant. The results from our correlation studies and factor analysis seemed to confirm the construct validity of the HNRN-33.

The limitations surrounding the HNRN-33 were similar to those encountered by most qualitative assessment tools. Respondent fatigue is a potential source of error and bias. The authors have attempted to limit this error by including less than 40 items in the HNRN-33, seen by several sources as the upper limit number of items before significant respondent fatigue is encountered. Inadequate comprehension of item statements can further propagate error. We attempted to minimize comprehension error by performing cognitive interviewing prior to the validation study's commencement. Ten head and neck oncology patients were asked to complete the itemized questionnaire out loud, and any further modifications to item wording were then made to facilitate comprehension. Further bias could also have been introduced into the HNRN-33 due to its response scale. The HNRN-33 uses a Likert-type scale and subsequently uses an ordinal response system. With only five response choices, instances may occur where no option serves as an adequate answer to the respondent. However, the literature did support the use of five response options, as a greater number of options often results in unused answer choices, and fewer introduces more error. Furthermore, some literature suggested that Likert-type scales may create more valid answers from patient responders.[16]

In summary, this is the first validation study of the HNRN-33. The results indicated that the HNRN-33 has strong correlations to commonly used and validated qualitative and objective assessments of function in head and neck cancer patients, which points to a significant level of validity of the HNRN-33 in the assessment of function. Additionally, the HNRN-33 is easily administered and, as evident in this study, can be used at multiple institutions. A further significant advantage of the HNRN-33 over several other qualitative functional assessment tools in head and neck cancer is the structured methodology employed to incorporate patients in its development. The structured use of patients in the development of a questionnaire where patients will be the primary respondents creates greater validity. The majority of head and neck functional questionnaires lack this crucial developmental process. Beyond incorporating patients in its development, the HNRN-33 methodology also prioritized the most important functional domains to head and neck cancer patients. The functional domains incorporated in the HNRN-33 can also be indicative of what domains should be included in a core-set of outcomes for head and neck cancer patients.

Future studies will focus on clinical correlation scoring of the HNRN-33: for example, to be able to associate specific scores with aspiration events. With more clinical data and focused studies, the HNRN-33 has the potential to be used as a screening tool for individuals at risk of aspiration who may require further evaluation.

6.5 CONCLUSION

The HNRN-33 is the first validated PRO instrument designed to assess functional outcomes in head and neck oncology patients and could serve as a single comprehensive

measure for functional outcomes. The HNRN-33 is easily transferable and administered at any facility and, therefore, has the potential to standardize outcomes.

Table 6-1: Phase IV Patient Demographics

Category	Numerical Value
Total participants	*N* = 25
Average age	62.6 years
Sex	14 male, 11 female
Primary tumor site	11 oral cavity, 9 oropharynx, 5 larynx

Table 6-2: Statistical Correlations to the HNRN-33

Domain	Outcome instrument compared to the E-33	Pearson's correlation coefficient, *r*	*p*-value of correlation coefficient
Swallowing	MBS (penetration-aspiration scale)	-0.60	0.002
Swallowing	MDADI	0.77	0.00001
Swallowing	EORTC-QLQ H&N35	-0.73	0.00005
Speech	Sentence intelligibility	0.55	0.049
Speech	Word intelligibility	0.61	0.027
Speech	SHI	-0.64	0.001
Dry mouth	EORTC-QLQ H&N35	-0.54	0.007
Chewing	EORTC-QLQ H&N35 (mouth opening)	-0.45	0.026
Chewing	EORTC-QLQ H&N35	-0.43	0.036

Table 6-3: Factor Analysis Patient Demographics

Category	Numerical Value
Total participants	*N* = 101
Edmonton participants	*N* = 49
NYC participants	*N* = 32
Turku participants	*N* = 20
Male	*N* = 65
Female	*N* = 36

Table 6-4: Factor Loading Values

Domain	Item #	Edmonton-NYC-Turku Factor loading value	*p*-value	Edmonton-NYC Factor loading value	*p*-value
Swallowing	1	0.78	<0.001	0.75	<0.001
Swallowing	2	0.87	<0.001	0.85	<0.001
Swallowing	3	0.81	<0.001	0.8	<0.001
Swallowing	4	0.6	<0.001	0.58	<0.001
Swallowing	5	0.83	<0.001	0.83	<0.001
Swallowing	6	0.34	<0.001	0.38	<0.001
Swallowing	7	0.56	<0.001	0.53	<0.001
Swallowing	8	0.59	<0.001	0.52	<0.001
Swallowing	9	0.83	<0.001	0.82	<0.001
Swallowing	10	0.8	<0.001	0.84	<0.001
Swallowing	11	0.79	<0.001	0.75	<0.001
Speech	12	0.77	<0.001	0.79	<0.001
Speech	13	0.65	<0.001	0.67	<0.001
Speech	14	0.69	<0.001	0.66	<0.001
Speech	15	0.73	<0.001	0.77	<0.001
Speech	16	0.78	<0.001	0.79	<0.001
Speech	17	0.77	<0.001	0.79	<0.001
Speech	18	0.87	<0.001	0.86	<0.001
Speech	19	0.86	<0.001	0.84	<0.001
Speech	20	0.74	<0.001	0.72	<0.001
Speech	21	0.69	<0.001	0.67	<0.001

Domain	Item #	Edmonton-NYC-Turku Factor loading value	*p*-value	Edmonton-NYC Factor loading value	*p*-value
Dry mouth	22	0.76	<0.001	0.84	<0.001
Dry mouth	23	0.91	<0.001	0.93	<0.001
Dry mouth	24	0.86	<0.001	0.86	<0.001
Dry mouth	25	0.43	<0.001	0.51	<0.001
Dry mouth	26	0.57	<0.001	0.58	<0.001
Dry mouth	27	0.64	<0.001	0.64	<0.001
Dry mouth	28	0.77	<0.001	0.77	<0.001
Chewing	29	0.65	<0.001	0.75	<0.001
Chewing	30	0.81	<0.001	0.78	<0.001
Chewing	31	0.91	<0.001	0.89	<0.001
Chewing	32	0.74	<0.001	0.71	<0.001
Chewing	33	0.72	<0.001	0.77	<0.001

Figure 6-1: FDA process of patient-reported outcome (PRO) design.

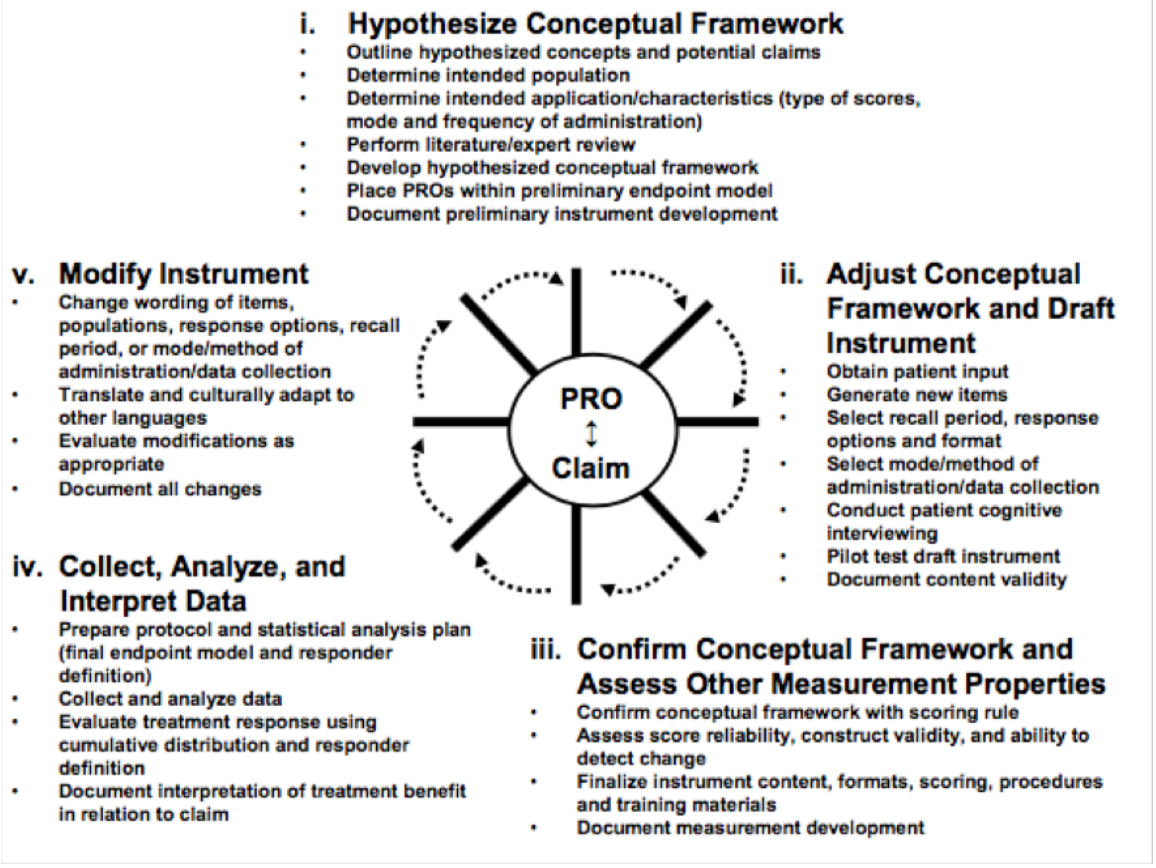


Figure 6-2: Swallowing—HNRN-33 vs MDADI scores, plotted per individual patient.

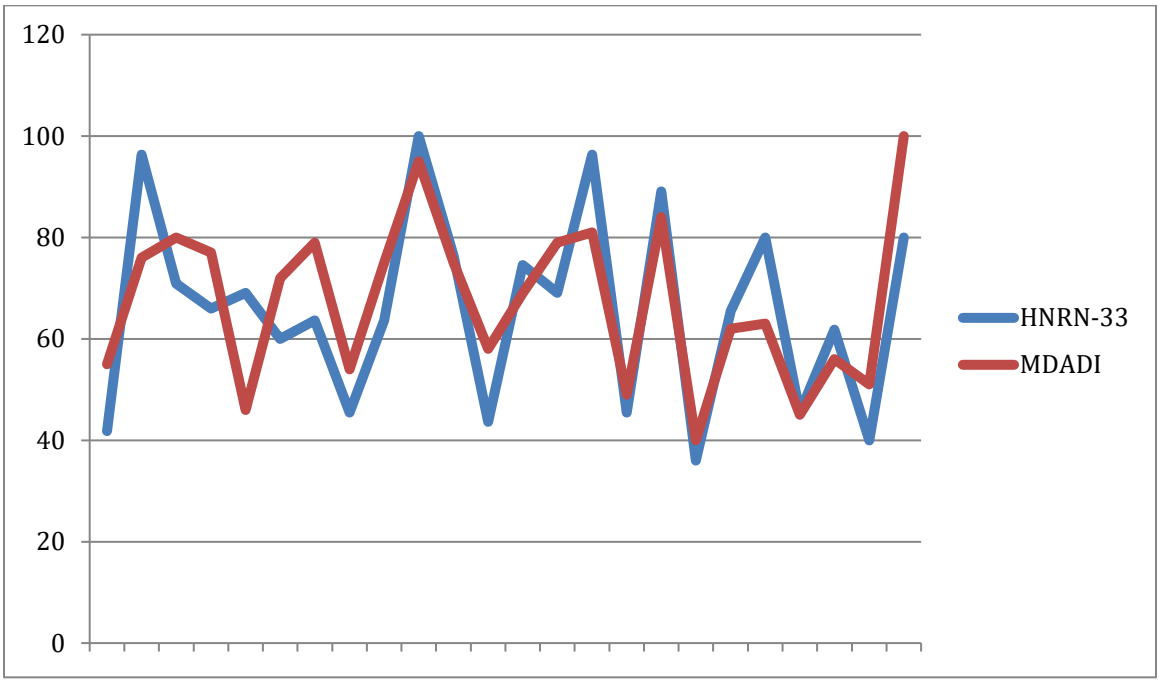


Figure 6-3: Swallowing—HNRN-33 vs EORTC scores, plotted per individual patient.

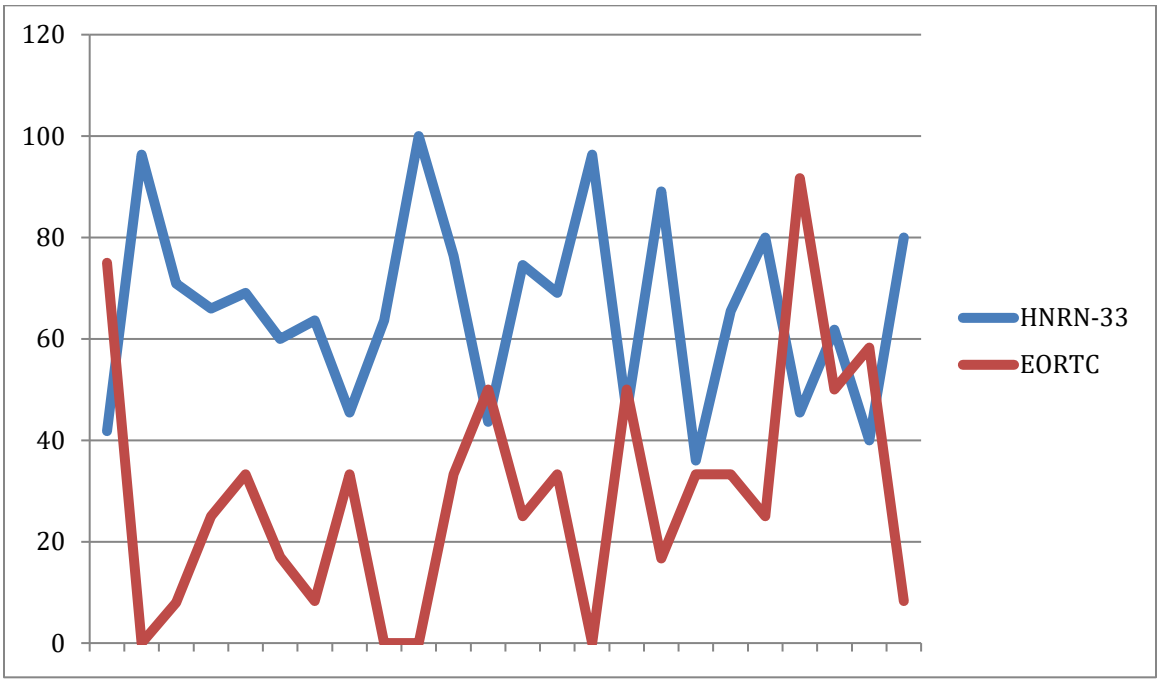


Figure 6-4: Factor loading value for swallowing.

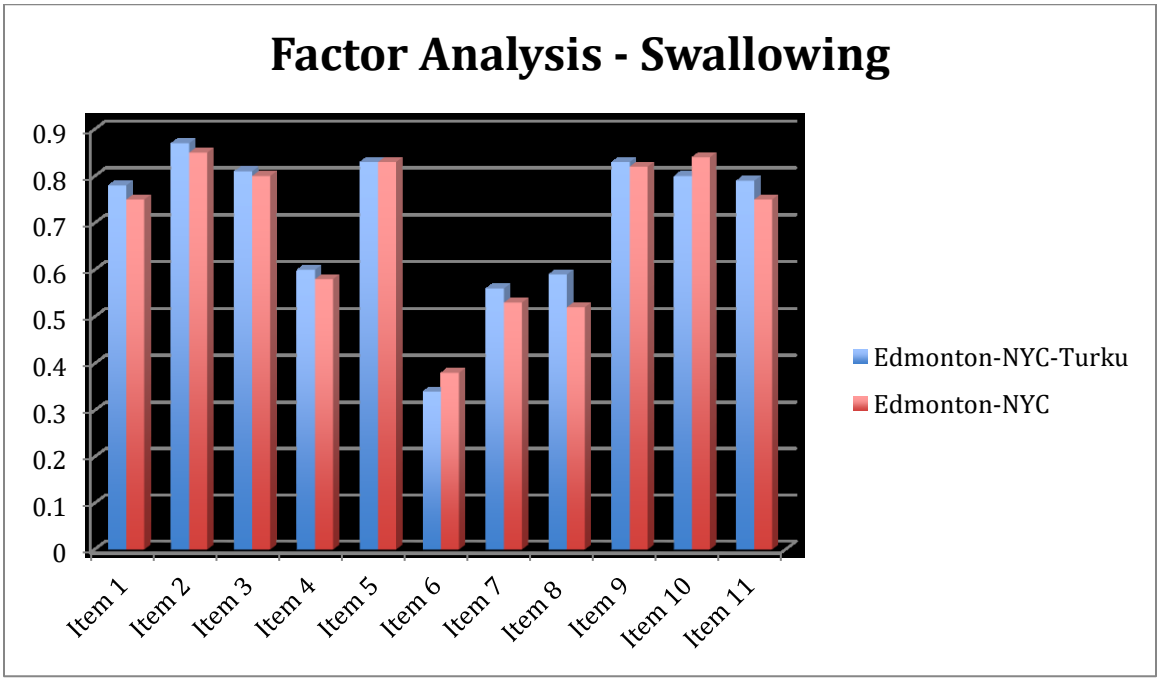


Figure 6-5: Factor loading values for speech.

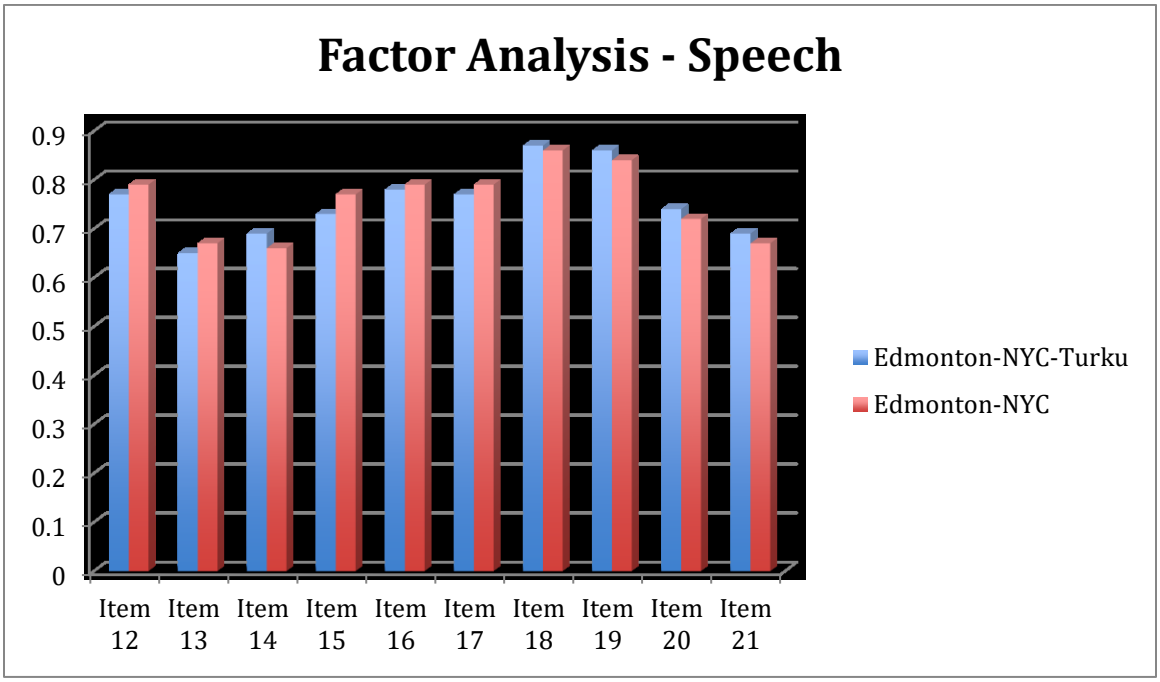


Figure 6-6: Factor loading values for dry mouth.

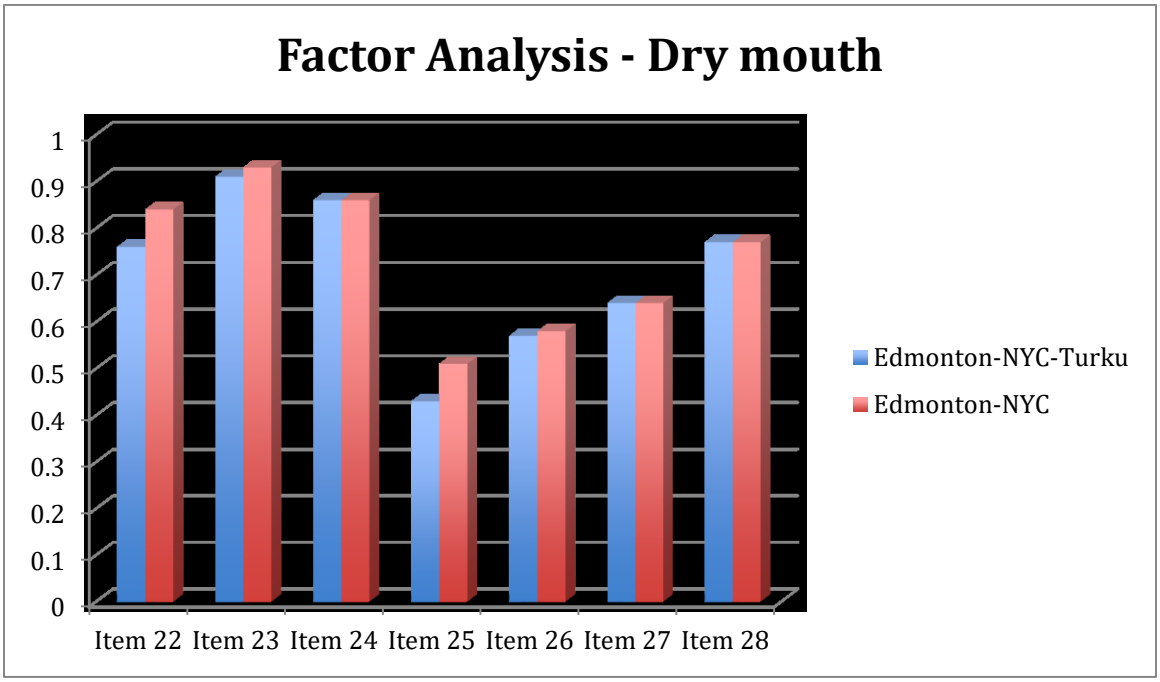


Figure 6-7: Factor loading values for chewing.

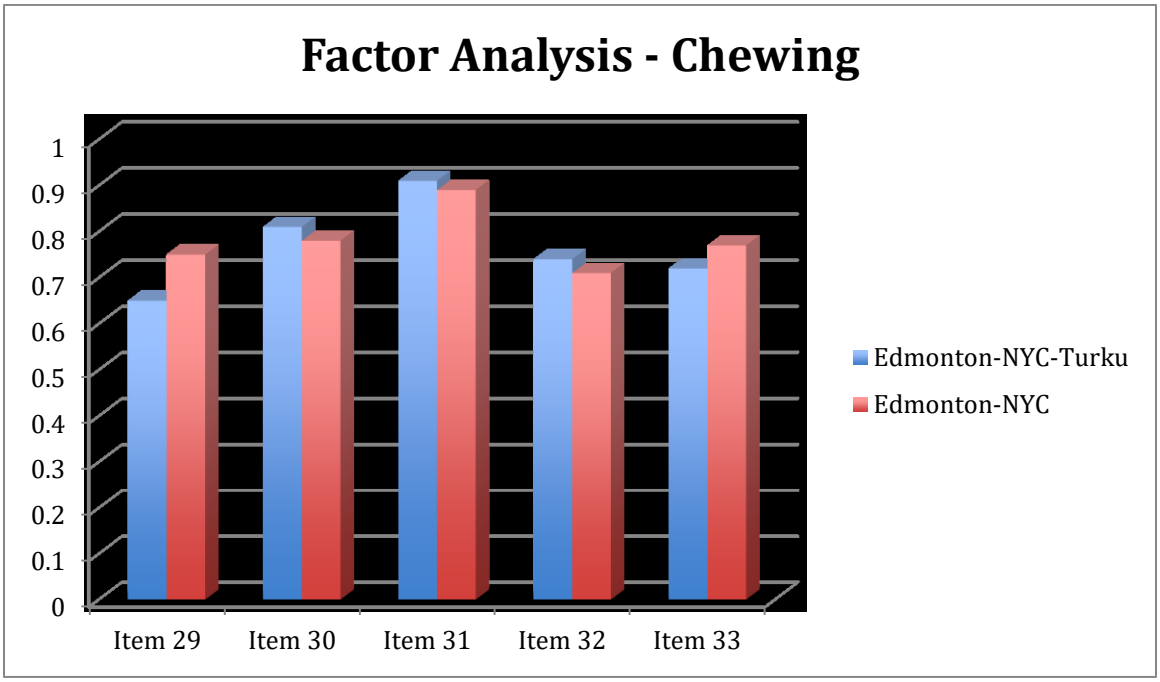
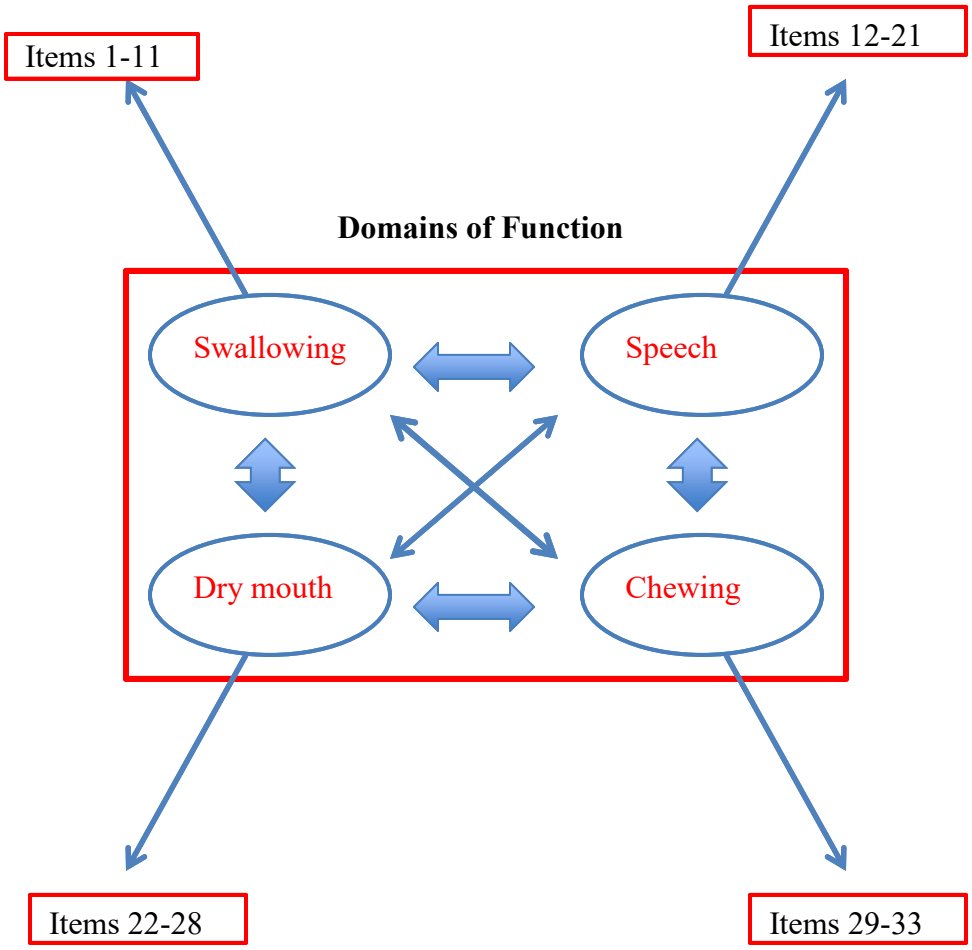


Figure 6-8: Factor loading conceptual diagram of the HNRN-33.



Appendix 6-1: The M.D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing. The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you. Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities

Strongly agree Agree No Opinion Disagree Strongly Disagree

E2. I am embarrassed by my eating habits

Strongly agree Agree No Opinion Disagree Strongly Disagree

F1. People have difficulty cooking for me.

Strongly agree Agree No Opinion Disagree Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly agree Agree No Opinion Disagree Strongly Disagree

E7. I do not feel self-conscious when I eat

Strongly agree Agree No Opinion Disagree Strongly Disagree

E4. I am upset by my swallowing problem

Strongly agree Agree No Opinion Disagree Strongly Disagree

P6. Swallowing takes great effort

Strongly agree Agree No Opinion Disagree Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly agree Agree No Opinion Disagree Strongly Disagree

F5. My swallowing difficulty has caused me to lose income

Strongly agree Agree No Opinion Disagree Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly agree Agree No Opinion Disagree Strongly Disagree

P3. People ask me, "Why can't you eat that?"

Strongly agree Agree No Opinion Disagree Strongly Disagree

E3. Other people are irritated by my eating problem

Strongly agree Agree No Opinion Disagree Strongly Disagree

P8. I cough when I try to drink liquids

Strongly agree Agree No Opinion Disagree Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly agree Agree No Opinion Disagree Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives

Strongly agree Agree No Opinion Disagree Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty

Strongly agree Agree No Opinion Disagree Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problem

Strongly agree Agree No Opinion Disagree Strongly Disagree

E6. I have low self-esteem because of my swallowing problem

Strongly agree Agree No Opinion Disagree Strongly Disagree

P4. I feel that I am swallowing a huge amount of food

Strongly agree Agree No Opinion Disagree Strongly Disagree

F4. I feel excluded because of my eating habits

Strongly agree Agree No Opinion Disagree Strongly Disagree

Appendix 6-2: The Speech Handicap Index

Instructions: These are statements that many people have used to describe their speech and the effects of their speech on their lives. Circle the response that indicates how frequently you have the same experience.

Note: 5 = Never, 4 = Almost Never, 3 = Sometimes, 2 = Almost Always, 1 = Always

	5	4	3	2	1
1. My speech makes it difficult for people to understand me	❍	❍	❍	❍	❍
2. I run out of air when I speak	❍	❍	❍	❍	❍
3. The intelligibility of my speech varies throughout the day	❍	❍	❍	❍	❍
4. My speech makes me feel incompetent	❍	❍	❍	❍	❍
5. People ask me why I'm hard to understand	❍	❍	❍	❍	❍
6. I feel annoyed when people ask me to repeat	❍	❍	❍	❍	❍
7. I avoid using the phone	❍	❍	❍	❍	❍
8. I'm tense when talking to others because of my speech	❍	❍	❍	❍	❍
9. My articulation is unclear	❍	❍	❍	❍	❍
10. People have difficulty understanding me in a noisy room	❍	❍	❍	❍	❍
11. I tend to avoid groups of people because of my speech	❍	❍	❍	❍	❍
12. People seem irritated with my speech	❍	❍	❍	❍	❍
13. People ask me to repeat myself when speaking face-to-face	❍	❍	❍	❍	❍
14. I speak with friends and neighbors or relatives less often because of my speech	❍	❍	❍	❍	❍
15. I feel as though I have to strain to speak	❍	❍	❍	❍	❍
16. I find other people don't understand my speaking problem	❍	❍	❍	❍	❍

	5	4	3	2	1
17. My speaking difficulties restrict my personal and social life	❍	❍	❍	❍	❍
18. The intelligibility is unpredictable	❍	❍	❍	❍	❍
19. I feel left out of conversations because of my speech	❍	❍	❍	❍	❍
20. I use a great deal of effort to speak	❍	❍	❍	❍	❍
21. My speech is worse in the evening	❍	❍	❍	❍	❍
22. My speech problem causes me to lose income	❍	❍	❍	❍	❍
23. I try to change my speech to sound different	❍	❍	❍	❍	❍
24. My speech problem upsets me	❍	❍	❍	❍	❍
25. I am less outgoing because of my speech problem	❍	❍	❍	❍	❍
26. My family has difficulty understanding me when I call them throughout the house	❍	❍	❍	❍	❍
27. My speech makes me feel handicapped	❍	❍	❍	❍	❍
28. I have difficulties to continue a conversation because of my speech	❍	❍	❍	❍	❍
29. I feel embarrassed when people ask me to repeat	❍	❍	❍	❍	❍
30. I’m ashamed of my speech problem	❍	❍	❍	❍	❍

Appendix 6-3: EORTC QLQ – H&N35[1]

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

Note: 1 = Not at all, 2 = A little, 3 = Quite a bit, 4 = Very much

During the past week:	1	2	3	4
31. Have you had pain in your mouth?	❍	❍	❍	❍
32. Have you had pain in your jaw?	❍	❍	❍	❍
33. Have you had soreness in your mouth?	❍	❍	❍	❍
34. Have you had a painful throat?	❍	❍	❍	❍
35. Have you had problems swallowing liquids?	❍	❍	❍	❍
36. Have you had problems swallowing pureed food?	❍	❍	❍	❍
37. Have you had problems swallowing solid food?	❍	❍	❍	❍
38. Have you choked when swallowing?	❍	❍	❍	❍
39. Have you had problems with your teeth?	❍	❍	❍	❍
40. Have you had problems opening your mouth wide?	❍	❍	❍	❍
41. Have you had a dry mouth?	❍	❍	❍	❍
42. Have you had sticky saliva?	❍	❍	❍	❍
43. Have you had problems with your sense of smell?	❍	❍	❍	❍
44. Have you had problems with your sense of taste?	❍	❍	❍	❍
45. Have you coughed?	❍	❍	❍	❍

During the past week:	1	2	3	4
46. Have you been hoarse?	❍	❍	❍	❍
47. Have you felt ill?	❍	❍	❍	❍
48. Has your appearance bothered you?	❍	❍	❍	❍
49. Have you had trouble eating?	❍	❍	❍	❍
50. Have you had trouble eating in front of your family?	❍	❍	❍	❍
51. Have you had trouble eating in front of other people?	❍	❍	❍	❍
52. Have you had trouble enjoying your meals?	❍	❍	❍	❍
53. Have you had trouble talking to other people?	❍	❍	❍	❍
54. Have you had trouble talking on the telephone?	❍	❍	❍	❍
55. Have you had trouble having social contact with your family?	❍	❍	❍	❍
56. Have you had trouble having social contact with friends?	❍	❍	❍	❍
57. Have you had trouble going out in public?	❍	❍	❍	❍
58. Have you had trouble having physical contact with family or friends?	❍	❍	❍	❍
59. Have you felt less interest in sex?	❍	❍	❍	❍
60. Have you felt less sexual enjoyment?	❍	❍	❍	❍

During the past week:	Yes	No
61. Have you used pain-killers?	❍	❍
62. Have you taken any nutritional supplements (excluding vitamins)?	❍	❍
63. Have you used a feeding tube?	❍	❍
64. Have you lost weight?	❍	❍
65. Have you gained weight?	❍	❍

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CHAPTER 7: SUMMARY

7.1 SUMMARY OF RESEARCH

The practice of medicine has fundamentally always been centered on patient care. As Sir William Osler famously stated, "The good physician treats the disease; the great physician treats the patient who has the disease."[1] Patient-centred care has led to the propagation of patient-centred outcome research, or prioritizing outcomes that are important to the individuals with the disease. A comprehensive treatment evaluation is now believed to include patients' perspectives of treatments in terms of patients' actual experiences.[2]

Patient-reported outcomes (PRO) have been developed in order to encapsulate the patient perspective in outcomes research. PROs often take the form of questionnaires, as direct patient report is considered to be the most reliable and accurate measure as well as being essential to patient-centredness.[3] Integral to the validity of PROs is the use of patients during conceptual formation and development.[4]

In Chapter 3, we performed a systematic review of PROs currently in existence in the head and neck cancer literature that pertain to the functional domains of swallowing, speech, chewing, and dry mouth, as these functional domains have been found to be prioritized by head and neck cancer patients, irrespective of treatment stage or primary sub-site. The results of this systematic review identified only two instruments that have been developed for patients with head and neck squamous cell carcinoma.[5,6] All other instruments were excluded, primarily because they did not use head and neck squamous cell carcinoma patients during their development or did not measure at least one of the

functional domains, including swallowing, speech, chewing, or dry mouth. The first instrument identified measured swallowing, but was valid only for laryngeal head and neck cancer patients. The second instrument measured dry mouth, but was valid only for head and neck cancer patients treated with primary radiation therapy.

Given the deficits in the literature, the objective of our study was to develop the first valid PRO instrument to measure the functional domains prioritized by head and neck cancer patients, using patients during the entirety of the developmental process. We developed a four-phase methodology, based on initial research outlined by pioneering patient-centred outcome research groups, including the US FDA and OMERACT.[7,8]

The objective of Phases I and II was to identify the functional domains prioritized by head and neck squamous cell carcinoma patients. Through grounded theory and a modified Delphi technique, swallowing, speech, chewing, and dry mouth were found to be the most important functional domains to patients. This confirmed the findings presented by Rogers et al. in their 2013 study.[9] Subsequently, the Head and Neck Research Network-33 (HNRN-33) was created in Phase III and was designed to measure these prioritized domains.

The objective of the final Phase IV study was to validate the HNRN-33. We wanted to demonstrate the validity of the HNRN-33 by correlating the instruments to both qualitative and objective measures of function. The design of the Phase IV study included correlation of the HNRN-33 against commonly used qualitative instruments in the literature, including the MD Anderson Dysphagia Inventory, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Head and Neck 35

(EORTC QLQ-H&N35), and the Speech Handicap Index (SHI). The HNRN-33 was also correlated against objective measures of function including the modified barium swallow and speech intelligibility. The results of Phase IV demonstrated good to strong correlation between all metrics. The correlation coefficients ranged from 0.43 to 0.77 and were all statistically significant.

In developing the HNRN-33, we attempted to follow the conceptual model of PRO instrument development created by pioneering research groups in this field.[7,8] The inclusion of patients at all stages of instrument development from conception to validation is a primary priority in creating valid PROs.[4] Our four-phase instrument development methodology has attempted to methodically and objectively include head and neck cancer patients. Although laborious and time consuming, we believe we have created the most valid PRO instrument to measure function in the head and neck cancer literature to date. In correlating the HNRN-33 to not only qualitative but also objective measures of function currently used in practice and research, we attempted to further strengthen the validity of the instrument and increase its utility. Finally, we further demonstrated the construct validity of the HNRN-33 by performing a large sample factor analysis and demonstrated that each individual item loaded onto the appropriate, intended domain. Each individual item has a factor loading value greater than 0.3 and is statistically significant. The advantage of the HNRN-33 over all other metrics of function in head and neck cancer are that it (1) incorporates the concepts of function prioritized by head and neck cancer patients themselves, (2) uses items and language prioritized and understood by both experts and patients, (3) has greater validity by using patients at all

developmental stages, (4) is valid against qualitative and objective methods of functional analysis, and (5) is transportable and easy to administer.

7.2 IMPLICATIONS FOR FUTURE RESEARCH

There is a need in comparative medicine and research to have standardized outcomes in order to compare different treatments to each other and, furthermore, to compare different treatments from different institutions to each other.[10,11] The OMERACT group has demonstrated, in rheumatology, that patient-centred outcome research (PCOR) is capable of developing a *core set* of outcomes.[12] These outcomes should always be measured for a particular pathologic process in order to standardize treatment analysis and facilitate comparison between treatments and institutions. PCOR is capable of demonstrating the outcomes that are prioritized by individuals with a particular pathologic process, and these outcomes, therefore, need to be considered in the core set. The development of the HNRN-33 highlighted that individuals with head and neck squamous cell carcinoma prioritized the functional outcomes of swallowing, speech, chewing, and dry mouth over all other; therefore, these outcomes should be considered in the creation of a core outcome set in head and neck cancer research.

The HNRN-33, in its entirety, should be viewed as a focused assessment of function for the head and neck cancer patient. The HNRN-33 encompasses four domains of function and can reduce patient as well as institutional burden, as patients could complete the HNRN-33 instead of individual clinical outcome assessments for each of these four domains (e.g., modified barium swallow, speech intelligibility, etc.). In this manner, the

HNRN-33 developed as a result of this research could serve as a screening tool for function in head and neck cancer patients.

Future studies for the HNRN-33 will involve the assessment of the HNRN-33 as a screening tool. Additionally, clinical correlation studies will be completed in order to attribute absolute scores on the HNRN-33 to specific clinical sequelae (e.g., aspiration events, g-tube use, etc.).

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