

**DEVELOPING BEST PRACTICE GUIDELINES FOR ORAL
CANCER MANAGEMENT IN MALAYSIA.**

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**FACULTY OF DENTISTRY
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KUALA LUMPUR**

2017

**DEVELOPING BEST PRACTICE GUIDELINES FOR
ORAL CANCER MANAGEMENT IN MALAYSIA**

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**THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF DOCTOR
OF DENTAL PUBLIC HEALTH**

**FACULTY OF DENTISTRY
UNIVERSITY OF MALAYA
KUALA LUMPUR**

2017

**UNIVERSITY OF MALAYA
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Field of Study: Community Dentistry

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ABSTRACT

Background: Quality of care at every stages of oral cancer management is crucial to achieve optimal cancer outcome and to improve quality of life of cancer patients. Enhancing the quality of care for oral cancer patients requires an evidence-based framework outlining the current and best practices in patient management. An evidence-based practice guideline can be used as a decision guide for oral cancer teams and cancer patients in selecting the best option of oral cancer care.

Aim: The aim of the study is to develop a best practice guideline for oral cancer management in Malaysia (which includes the stages of diagnosis, treatment, and follow-up care) for use by healthcare professionals managing oral cancer patients in the country.

Methods: The concept of “Guideline Adaptation” was used in the development of the Malaysian guideline. The core methodologies used were reviewing of high quality evidence and adoption as well as adaptation of recommendations from the existing guidelines, blended with expert judgements from a multidisciplinary group. Following the Practice Guidelines Evaluation and Adaptation Cycle (PGEAC), the guideline development process consists of six steps: i) identify clinical areas to promote best practice, ii) literature search to identify existing guidelines, iii) assessment of the guidelines in terms of quality, currency, and content, iv) adopt or adapt guidelines for local use v) seek multidisciplinary specialists feedback and vi) finalising best practice guidelines.

Results: Initially, fifteen potential existing guidelines were selected through a systematic literature search. Of the fifteen guidelines, three guidelines that were developed by the Comprehensive Cancer Network (NCCN), Belgian Health Care

Knowledge Centre (BKCE) and Scottish Intercollegiate Guideline Network (SIGN) were selected based on their good performance in the quality assessment using the AGREE II instrument. As the currency assessment revealed that all the three shortlisted guidelines were still up-to-date, these guidelines were considered the most appropriate to be included in the development of the local guidelines. On the basis of content analysis, the expert panel agreed to adopt 81 recommendations from the three guidelines whereas 10 recommendations were accepted with modification and one new recommendation was added to the draft guidelines. The draft version of the Malaysian guidelines comprised three sections (Section 1: Introduction, Section II: Development of the guidelines and Section III: eighty-eight clinical recommendations and summary of the evidence) and an algorithm of the whole process of oral cancer management. In response to the specialists' feedback, some minor changes and an additional recommendation were made to the draft. The final 47-pages Malaysian guidelines comprised three similar sections as in the draft, eighty-eight recommendations, an algorithm, and clinical audit indicators for quality management.

Conclusion: The comprehensive Malaysian guideline with a final number of 88 recommendations was produced through a rigorous process in an attempt to cover all aspects of oral cancer management. Adherence to the guidelines in managing oral cancer patients in this country is expected to improve the quality of care and health outcome of the cancer patients.

ABSTRAK

Latarbelakang: Kualiti penjagaan pesakit pada setiap peringkat pengurusan kanser mulut adalah penting untuk mencapai hasil yang optimum dan meningkatkan kualiti hidup pesakit. Untuk meningkatkan kualiti penjagaan pesakit kanser mulut, rangka kerja yang berasaskan eviden terkini adalah diperlukan. Garis panduan amalan terbaik berasaskan eviden terkini boleh diguna pakai oleh perawat dan pesakit kanser sebagai panduan dalam membuat pilihan terbaik bagi penjagaan kanser mulut.

Tujuan kajian: Tujuan kajian ini adalah untuk menghasilkan garis panduan bagi amalan terbaik berdasarkan bukti terkini untuk pengurusan kanser mulut di Malaysia yang merangkumi diagnosis, rawatan dan penjagaan susulan, untuk di guna pakai oleh kakitangan kesihatan yang menguruskan pesakit kanser di negara ini.

Metodologi: Konsep *Guideline Adaptation* telah digunakan dalam penghasilan garis panduan ini. Metodologi teras yang digunakan adalah mengenal pasti bukti yang berkualiti tinggi, adaptasi cadangan klinikal daripada garis panduan sedia ada digabungkan dengan keputusan daripada kumpulan kepakaran pelbagai disiplin. Berdasarkan *Practice Guidelines Evaluation and Adaptation Cycle (PGEAC)*, proses penghasilan garis panduan ini terdiri daripada enam langkah: i) mengenal pasti bidang klinikal untuk menggalakkan amalan terbaik, ii) sorotan literatur untuk mengenal pasti garis panduan sedia ada, iii) penilaian garis panduan dari segi kualiti, maklumat terkini dan isi kandungan iv) menyesuaikan garis panduan untuk kegunaan tempatan, v) mendapatkan maklum balas daripada pakar pelbagai disiplin dan vi) memuktamadkan garis panduan amalan terbaik.

Keputusan kajian: Lima belas garis panduan sedia ada yang berpotensi untuk digunakan dalam kajian ini telah dikenal pasti melalui sorotan literatur. Dari lima belas

garis panduan tersebut, tiga garis panduan yang dihasilkan oleh *Comprehensive Cancer Network (NCCN)*, *Belgian Health Care Knowledge Centre (BKCE)* and *Scottish Intercollegiate Guideline Network (SIGN)* telah dipilih berdasarkan prestasinya yang baik dalam penilaian kualiti menggunakan alat penilaian *AGREE II*. Hasil penilaian mendapati garis panduan-garis panduan ini mengandungi bukti yang terkini dan masih sesuai digunakan, ketiga-tiganya telah didapati sesuai untuk digunakan bagi penghasilan garis panduan tempatan. Berdasarkan analisis terhadap isi kandungannya oleh ahli panel yang terdiri daripada pelbagai kepakaran, 81 cadangan daripada tiga garis panduan tersebut diterima tanpa perlu pengubahsuaian, manakala 10 cadangan telah diterima dengan pengubahsuaian dan satu cadangan baru telah ditambah kepada draf garis panduan tempatan. Pada umumnya, draf garis panduan tempatan terdiri daripada tiga bahagian utama (Bahagian 1: Pengenalan, Bahagian II: Penghasilan Garis Panduan dan Bahagian III: 88 cadangan pengurusan klinikal dan ringkasan bukti yang menyokong cadangan tersebut) dan algoritma keseluruhan proses pengurusan pesakit kanser mulut. Akhirnya, garis panduan tempatan yang terdiri daripada 47 halaman yang terbahagi kepada bahagian yang sama seperti dalam draf, 88 cadangan pengurusan klinikal, algoritma, dan indikator klinikal bagi audit pengurusan kualiti telah dihasilkan berdasarkan maklum balas daripada sekumpulan pakar pelbagai disiplin yang berpengalaman dalam pengurusan pesakit kanser mulut di negara ini.

Kesimpulan: Garis panduan tempatan yang terdiri daripada 88 cadangan telah dihasilkan melalui proses yang teliti dalam usaha untuk merangkumi semua aspek pengurusan kanser mulut. Pematuhan kepada garis panduan ini dijangkakan dapat manambah baik kualiti penjagaan dan kesihatan pesakit kanser di negara ini.

ACKNOWLEDGEMENTS

In the name of **Allah SWT**, Who has given me the strength to complete this study. The successful and completion of this study is very much due through the help and support from everyone. I would like to express my deepest appreciation to the following who had contributed to the undertaking and completion of this study:

- My supervisors, Assoc. Prof Dr Jennifer Gerald Doss and Professor Dato' Prof Ishak bin Abdul Razak for their patience, continuous guidance, encouragement and invaluable detailed advised during the whole process of this study.
- The current dean, Professor Dato` Dr. Zainal Ariff Bin Abdul Rahman, for the support and encouragement given.
- Assoc. Prof Dr. Zamros Yuzadi Mohd Yusof, Head of Department, Prof Nasruddin Jaafar, Prof Datin Dr. Rashidah Esa, Prof Dr. Roslan Saub, Assoc Prof Dr. Norintan Abdul Murat and Dr. Asma' Mohamed for sharing their knowledge, advice and guidance throughout the course.
- Expert panel members of the clinical content analysis, multidisciplinary specialists involved in the Focus Group Discussion (FGD) and the source guideline developers (The Scottish Intercollegiate Guideline Network, Belgian Health Care Knowledge Centre and National Comprehensive Cancer Network) for their contributions towards the development of the Malaysian guideline.
- The Director of Oral Health Services of Malaysia, Datuk Dr. Noor Aliyah bt Ismail, Dr Yaw Siew Lian, Dr Nurrul Ashikin Abdullah, DSA Sarina Othman for the support given to me in the process of conducting FGD during this study.
- My colleague, Azlina Hashim, who had shared many memorable memories and support throughout the course and may our friendship remains forever.

- To my late father, mother, mother in law and father in law for their concern, moral support and prayers.
- To my beloved husband, Fazrel Shahiri and my precious children, Alya Farhana, Arif Fikri and Amir Fikri for their patience over the years and without their support and encouragement, I would not have been able to pursue and complete my postgraduate study.
- To all others who I have not mentioned here and who were involved directly or indirectly in my study, may Allah bless you all.

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LIST OF ABBREVIATIONS

OSCC	Oral Squamous Cell Carcinoma
CT	Computed Tomography
IMR	Magnetic Resonance Imaging
FDG-PET/CT	Fluorodeoxyglucose Positron Emission Tomography- Computed Tomography
EUA	Examination under anaesthesia
HPV	Human Papillomavirus
USFNAC	Ultrasound-guided fine-needle aspiration cytology
OPG	Panoramic oral radiograph
PS	Performance status
WPOI	Worst pattern of invasion
HR	Hazard ratio
RT	Radiotherapy
CRT	Chemotherapy
RCT	Randomized control trial.
OTTRT	Overall treatment time of radiation
LRC	Locoregional control
TPP	Total treatment package
PGEAC	The Practice Guideline Evaluation and Adaptation Cycle
AGREE	The Appraisal of Guidelines for Research and Evaluation
EBD	Evidence-based practice
CPGs	Clinical Practice Guidelines
BPGs	Best Practice Guidelines

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CHAPTER 1: INTRODUCTION

1.1 Problem Statement

Oral cancer is part of head and neck cancers and it is a significant medical burden in many parts of the world (American Cancer Society, 2011). Worldwide, oral and pharyngeal cancer grouped together, is the sixth most common cancer. The annual estimated incidence of oral cancer is around 275,000 with two-thirds of these cases found in developing countries (Warnakulasuriya, 2009). In Malaysia, based on the National Cancer Registry (2007-2011) tongue and mouth cancer incidence was ranked among the 20th most common cancer in the general population (Manan et al., 2016). Oral cancer has one of the lowest survival rates, and the important determinant for cancer survival are the diagnostic delay and ineffective treatment at the advanced stage of cancer (Brocklehurst et al., 2013).

Advances in prevention, diagnosis, and treatment for cancer have improved survival of cancer patients (Gotay & Muraoka, 1998; Bower et al., 2014). The global five-year survival rate for all cancers in the UK is 50% with survival rates for some malignant melanoma such as the cancers of the breast, uterus and thyroid being as high as 80% (American Cancer Society, 2011; Cancer Research UK, 2014). Head and neck cancer, including oral cancer patients, have also reaped the benefit from these advances resulting in an increasing number of oral cancer survivors in our community.

The increasing number of survivors presents a challenge for oral cancer management. The diagnosis and treatments that have enabled long-term survival, however, is associated with a significant physical burden such as facial disfigurement,

difficulty in swallowing and communication (Alshadwi et al., 2013; Good et al., 2014a; Good et al., 2014b) frequent co-morbidities, and psychosocial sequelae to the patients which can have a negative impact on their quality of life (Mehanna & Morton, 2006; Mehanna et al., 2010; Luckett et al., 2011; Scott et al., 2013; Semple et al., 2013). The quality of care at every stage of cancer management is crucial in achieving optimal cancer outcome and to improve the quality of life of the cancer survivors (Moore et al., 2014). Treatment is usually a combination of surgical removal, radiotherapy or chemotherapy. Also, supportive care has been identified as an essential component in the management of cancer patients, in order to meet the needs of both patients and their families throughout the treatment phases (Fadul et al., 2009; Richardson et al., 2014). Patients with oral cancer require professional support including physical, psychological, social, spiritual, health information, and interpersonal communication in coping with the treatment consequences (Adelstein et al., 2003; Balboni et al., 2011; Scott et al., 2013; Moore et al., 2014; Pateman et al., 2015).

Enhancing the quality of care for oral cancer patients requires an evidence-based framework outlining the current and best practices in patient management. Evidence-based guidelines provide oral cancer teams and cancer patients with the best option for cancer care and should be part of these best practices to ensure the quality of care and patients outcomes are optimized (Grimshaw et al., 1995b; Shaneyfelt et al., 1999). The development of high quality evidence-based practice guidelines should involve a multidisciplinary group of experts in identifying and analysing the highest quality evidences and formulating the recommendations, with essential feedback from health care professionals managing oral cancer patients, within the context in which they will be implemented (Browman, 2001; Davis et al., 2007). Properly developed practice guidelines may offer optimal treatment strategies for the health professional according

to local circumstances, available resources and patients' needs and preferences (Green & Piehl, 2003).

1.2 Rationale of the Study

Practice guidelines are being increasingly recognized as critically important to an evidence-based practice. Several recognized organisations worldwide such as the French National Federation of Cancer Centres (Browman, 2001), Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network (SIGN), 2006) and National Comprehensive Cancer Network (National Comprehensive Cancer Network, 2014) have set up multidisciplinary working teams and developed evidence-based clinical practice guidelines in the management of their cancer patients.

Currently in Malaysia, only Clinical Practice Guideline (CPG) on Primary Prevention and Early Detection of Pre-cancerous and Oral Cancer is available (Ministry of Health Malaysia, 2002). Hence, healthcare professionals manage their oral cancer patients from the point of diagnosis, treatment, and follow-up care differently, based on their individual training or by the different international guidelines they prefer. Best practice guideline that address the full continuum of oral cancer management have yet to be formalized for the healthcare professional to use in a standardized manner to effectively manage oral cancer patients in our country

Although a number of guidelines on the same topics have been developed by other recognised organisations, the use of those guidelines in this country may not necessarily be appropriate without modification (Fervers et al., 2011). The cultural and organisational differences between countries can lead to potential difficulties for implementation of the guideline's recommendations in the local practice. A local study

on head and neck multidisciplinary team reported that some of the team members believed that there is a need to develop guidelines specifically for Malaysia (Alobaidi, 2016). Needless to say, there is a strong indication for such a guideline to be developed in Malaysia.

As the development of a new evidence-based practice guideline would involve a rigorous process and require a lot of time and resources, the “Guideline Adaptation” concept is used in this study as an alternative to the *de novo* development. Guideline adaptation is a systematic approach for customizing existing guidelines by adopting or adapting the recommendations to suit the local context (Graham et al., 2002; Graham & Harrison, 2005). Furthermore, adaptation of guidelines is increasingly being considered by several guidelines developers such as New Zealand Guideline Groups and American Society of Clinical Oncology, particularly to avoid unnecessary duplication of effort and to optimize the use of resources in the development process (Fervers et al., 2006; Schünemann et al., 2006).

1.3 Aim of the Study

This study aimed to develop best practice guideline for oral cancer management in Malaysia for use by healthcare professional managing oral cancer patients in the country. Best practice guideline for prevention and screening is beyond the scope of this study, since Clinical Practice Guideline (CPG) on Primary Prevention and Early Detection of Pre-cancerous and Oral Cancer is already available and in the midst of an on-going review by the Oral Health Division, Ministry of Health Malaysia.

1.4 Objectives of the Study

1. To review existing ‘best practice guidelines’ and ‘systematic reviews’ published since the preparation of the latest selected guidelines on oral cancer management.
2. To prepare a guidelines draft for oral cancer management in Malaysia.
3. To obtain feedback from a multidisciplinary specialists regarding the draft guidelines for oral cancer management in Malaysia.
4. To formulate best practice guidelines for oral cancer management in Malaysia including diagnosis, treatment, and follow-up care.

University of Malaysia

CHAPTER 2: LITERATURE REVIEW

This chapter is divided into five main sections as follows:

- 2.1 Review on oral cancer, including the classification, aetiology, epidemiology and the principle management of oral cancer.
- 2.2 The approaches to evidence-based practice and how evidence-based practice guideline is incorporated in cancer management.
- 2.3 The concept of guideline development which covers both the De Novo Guideline Development and Guideline Adaptation Concept.
- 2.4 The quality assessment of the guideline which covers several features of the instruments particularly the AGREE instrument.
- 2.5 The description of the focus group discussion as a qualitative approach to obtain expert judgment and group consensus.

2.1 Oral Cancer

2.1.1 Classification of Oral Cancer

Oral cancers are defined as malignant tumours of the oral cavity. It affects the structures or tissues of the mouth including the tongue, gingivae, buccal mucosa, retromolar trigone, hard palate, lip and floor of the mouth (Ministry of Health Malaysia, 2002; Scottish Intercollegiate Guidelines Network, 2006; Alberta Health Services, 2014). The classification of oral cancers in accordance with the current revised ICD-10, coding of the international classification of diseases by World Health Organization (1999) are listed in Table 2.1 (Pine & Harris, 2007). The most common form of oral cancers reported was primary oral mucosal squamous cell carcinoma (OSCC) (>90%). The remainder will be salivary gland neoplasm, lymphomas, malignant melanomas,

sarcomas, and secondary tumor. The most common site for oral cancer is the tongue followed by the floor of the mouth (Brown & Langdon, 1995; Neville & Day, 2002; Mehrotra & Yadav, 2006)

Table 2.1: ICD10 Classification of Oral Cancer

ICD Code	Terms of oral cancer
ICD-10 C00	squamous cell carcinoma
ICD-10 C01/02	tongue
ICD-10 C03	gingiva
ICD-10 C04	floor of mouth
ICD-10 C05	palate
ICD-10 C06	other and unspecified part of the mouth
ICD-10 C09	tonsil
ICD-10 C13	oropharynx
ICD-10 C14	other ill-defined sites in the lip, oral cavity, and pharynx

2.1.2 Aetiology and Pathology of Oral Cancer

Oral cancer may originate as pre-malignant or may develop de novo as a primary lesion in the mouth (Johnson et al., 2011; Kerawala et al., 2016). The common forms oral potentially malignant disorders (OPMD) are leukoplakia, erythroplakia, lichen planus and submucous fibrosis (Pine & Harris, 2007). Worldwide, the prevalence of OPMD ranged from 1.0% to 13.9%. Leukoplakia is the most prevalent (OPMD) found in the oral mucosa (0.7%-24.8%) followed by lichen planus (0.1%-2.9%), erythroplakia (0.4%-1.9%) and oral submucous fibrosis (0.06%-1.6%). Despite its high prevalence,

only 0.13% to 6.0% of leukoplakia had transformed into a malignant lesion. In contrast, oral submucous fibrosis are less common with prevalence of less than 2.0% but it has a greater tendency towards malignant transformation (3.0%-19%) (Mashberg & Samit, 1989; Sudbo & Reith, 2003; Petersen et al., 2005; Johnson et al., 2011; Garg et al., 2013).

Oral cancer often present clinically as a white or red patch and do not usually cause any symptom at the initial stage of the disease. As the lesion grows, superficial ulceration of the mucosal surface may develop. With time, the lesion may present as an exophytic mass. Other tumours have an endophytic growth pattern which appears as a depressed ulcerated surface with a raised, rolled border (Neville & Day, 2002; Viviano et al., 2013). Advance tumours can present with an invasion of neighbouring structures (Kerawala et al., 2016). Oral cancers usually spread from the primary tumour through lymphatic system of the neck or by direct extracapsular pathways and from there metastases to other parts of the body, such as the lungs, bone, liver and brain (Pigadas & Jevon, 2014).

2.1.3 Risk Factors of Oral Cancer

The majority of the oral cancers are linked with several risk factors such as heavy consumption of alcohol, tobacco use in various forms, and betel quid or areca nut chewing. Strong correlation between those habits and the presence of oral cancer lesions has been reported in the previous studies. Duration and intensity of those habits were found to be closely related to the increased risk of oral cancer (Mashberg & Samit, 1989; Aruna et al., 2011; Gupta et al., 2014; Wang et al., 2015)

Increased tobacco and alcohol consumption in developed countries have been identified as the leading risk factor for the development of oral cancer in these countries (International Agency for Research on Cancer, 2004). The carcinogenicity of nicotine-derived nitrosamine ketone (NNK), N-nitrosornicotine (NNN) and polycyclic aromatic hydrocarbons in tobacco and ethanol contained in the alcohol exerted through (deoxyribonucleic acid) DNA adducts and may be part of the causal chain for malignant transformation. Previous studies that quantified the risk of oral cancer indicated that the odds of tobacco smokers getting oral cancer are 3.43 to 19.8 times greater than those who had never smoked and the odd ratios ranged from 1.21 to 13.03 for those who consumed alcohol. The interaction of tobacco and alcohol may cause a synergistic mechanism and leads to a greater effect. Ethanol in the alcohol damages the phospholipids of cell membranes and enhances the penetration of tobacco-specific carcinogens across the oral mucosa. Therefore, people with dual habits of smoking and consumed alcohol were reported at greater risk (8.9 times) to develop oral cancer as compared to people with independent habits of smoking or alcohol (Talamini et al., 2002; Johnson et al., 2011; Wolff et al., 2012).

On the other hand, smokeless tobacco products and betel quid chewing are considered to be important risk factors for oral cancer in the South-Asian Countries (Daly et al., 2007; Lim et al., 2008). The addition of areca nut, slaked lime or tobacco to the quid is the critical factor. Nitrosamine produced in the dried areca nuts is a well-known carcinogen for the malignant transformation of the oral cavity cancer. The addition of slaked lime to the betel quid may erode the oral mucosa, thus enhances the penetrations of carcinogens through the mucosa. There are evidence to support that people with betel quid chewing (with or without tobacco) had a greater risk of getting oral cancer as compared to those without the habit (odds ratio of 3.5 (95% CI 2.16-5.65)

(Johnson et al., 2011) and (relative risk RR of 5.5 (95% CI 3.07-9.85). Tobacco chewing carries a higher risk than smoking, possibly due to the enhanced topical effect of Tobacco-specific N-nitrosamines in smokeless tobacco (Yen et al., 2007; Gupta et al., 2014)

Beside established risk factors that had been discussed above, dietary factors (Vitamin A, C, E and Iron deficiencies and high consumption of beverages, starches, dairy and fermented/salted food), genetic predisposition, occupation hazard or sunlight, human papilloma virus and dental irritation are thought to be the predisposing factors for oral cancer. However, their effects are still lacking and not adequately explain in OSCC (Mehrotra & Yadav, 2006; Daly et al., 2007; Helen-NG et al., 2012).

2.1.4 Epidemiology of Oral Cancer

In many parts of Asia, oral cancer was ranked among the top 10 cancers and more than half of the world's oral cancer cases were found in Asia (Warnakulasuriya, 2009). Oral cancer is the most common type of cancer in the region, accounting for 40% of all cancer as compared to 1-2% in the United Kingdom (Winter et al., 1999; Daly et al., 2007). Based on GLOBOCAN 2008, produced by International Agency for Research on Cancer (IARC), Malanesia, South-Central Asia experienced the highest oral cancer incidence rate. The ASR for male/female in Malanesia and South-Central Asia are 24.0 /12.0 per 100,000 population and 9.4/5.5 per 100,000 population respectively (International Agency for Research on Cancer, 2010).

Based on age-standardised rate (ASR) per 100,000 world standard population, more men are affected with oral cancers compared to women in the West whereas the disease is distributed almost equally between men and women in most of the Asian Countries

(World Health Organization, 2005). The reported incidence rate in the West ranged from 4.40 to 32.2 and 1.96 to 6.1 per 100,000 populations for men and women respectively. In contrast, the ASR (14.69/ 100,000 populations) for man in Pakistan was similar to the women (14.72/100,000 population) (Ferlay et al., 2001).

Oral cancer was found predominantly in older people (50years and above) and the incidence increases steadily from the age of 30 years upwards. However, the number of young adults developing oral cancer lesions is increasing especially in the high-incidence countries in the last time periods (Macfarlane et al., 1994; Howell et al., 2003; Shiboski et al., 2005). The tongue is the most common site found in the United States and Europe while buccal mucosa is the more common site affected among the Asian population due to betel quid/tobacco chewing habits (Ministry of Health Sri Lanka, 2005).

For most countries, the average five-year survival rates for oral cancer are around 50% and the age-adjusted death rates have been estimated at 3-4 per 100,000 men and 1.5-2.0 per 100,000 women. The low survival rate is largely reflected by the delay in the detection of the disease (Warnakulasuriya, 2009). At the later stage, oral carcinoma has a negative prognosis due to the capacity of the disease to metastasise in the lymph nodes of the necks and in the lung (Berrino, 2003). Five-year survival rates reach 80%-90% in cases with early diagnosis as compared to only 20% in stages III and IV cases and less than 10% for the patient with distant metastases (Viviano et al., 2013; Pigadas & Jevon, 2014). Based on the site of the lesion, cancer of the lip presented the highest five years survival rate (90%) and the lowest was soft palate cancer due to inaccessibility of the tumour (Warnakulasuriya, 2009).

Despite the increasing trend in the number of oral cancer in the United Kingdom (UK) during the last three decades (1984: 1912 cases, 2011: 6767 patients), significant decreases in mortality have been observed among males. Moreover, the ratio of males to females diagnosed with oral cancers has declined from approximately 5:1 in the 1960s to less than 2:1 in 2002 (Banoczy & Squier, 2004; Parkin et al., 2005; Jemal et al., 2011).

In Malaysia, the National Cancer Registry (2007-2011) reported that tongue and mouth cancer incidence was ranked among the 20th most common cancer in the general population (Manan et al., 2016). Based on the former report in 2008, one new case of oral cancer is diagnosed daily. The prevalence is found to be predominantly among some identified communities. Sixty-percent of oral cancer cases are seen among the ethnic Indians community although they only comprise about 8% of the population (Ministry of Health Malaysia, 2002; Helen-NG et al., 2012). Mouth and tongue cancers have been found as the 10th most common cancers among Indians. The incidence was highest among Indian females of which the ASR was 7.5/100,000 populations. The lowest incidence rates were found among Malay male and Chinese female with the ASR was 0.4/100,000 population. A major concern was that more than 50% of the cases were detected at a late stage and the prognosis decreases with advanced diseases (Manan et al., 2016). Based on the data published in 2011 by the World Health Organization (WHO), oral cancer deaths in Malaysia was about 1587 or 1.55% of total deaths. The age-adjusted death rate is 7.72 per 100,000 of the population in which ranks Malaysia 14th in the world (Oral Cancer Research and Coordinating Centre, 2017).

2.1.5 Management of Oral Cancer

Generally, the aim of oral cancer management is to eliminate the tumour and any neck nodal metastases, with minimum morbidity to the patient (Brown & Langdon, 1995). Treatment outcome and survival for oral cancer will depend on several factors including the site and size of the lesion, histology or degree of differentiation, regional lymph nodes involvement and presence of distant metastases. Generally, the ability to detect the lesion at a very early stage is crucial for the effective treatment of the disease and improved survival of the patients (Daly et al., 2007).

2.1.5.1 Multidisciplinary Care for the Management of Oral Cancer

Oral cancer is best managed by multidisciplinary teams (MDTs) because of the complexity of the treatment modalities required for the cancer patients. The multidisciplinary care brings together a group of health professionals from different disciplines to plan and provide the best care for cancer patients. Evidence has shown that the MDT approach has been able to address some issues in cancer care in terms of patients' tolerability to the treatment, availability of resources and quality of life of the patients (Ord & Blanchaert, 2001; D'cruz et al., 2013).

Previous studies demonstrated that the management of head and neck cancer by MDT approach have significantly shorter interval time between surgery and radiotherapy, reduced the mean length of hospitalization and improved clinical decision as well as survival of stage IV patients (Wheless et al., 2010; Friedland et al., 2011; Kelly et al., 2013). A local qualitative study done by Alobaidi (2016) reported that the MDT members perceived that the MDT approach had improved coordination of care for cancer patients, communication and decision making between various different

disciplines. However, further improvement is needed with regards to the expansion of the current team composition, training of the MDT members in terms of clinical and nonclinical skills, guidelines, protocols and availability of resources.

According to several guidelines for head and neck cancer, the multidisciplinary team should include both core-members of MDTs as well as non-core members. In reality, it is difficult to get all the team members together at the same time for each individual patient. The core members of MDTs who are the main players for every patient may include a number of specialists from different disciplines comprising an Oral and Maxillofacial Surgeon, Otorhinolaryngologist, Pathologist, Clinical Oncologist, Radiologist and Plastic Surgeon. The non-core members should assume an important position in the MDT particularly for pre-treatment, follow-up and supportive care. The non-core members may include a Dentist, Nurses, Speech and Swallowing Therapist, Nutritionist and Psychosocial Workers (Neville & Day, 2002; Scottish Intercollegiate Guidelines Network, 2006; Belgian Health Care Knowledge Centre, 2014a; National Comprehensive Cancer Network, 2016).

2.1.5.2 Principle of Oral Cancer Management

a. Diagnosis and Staging

Diagnosis and staging of oral cancer are important processes in assessing the prognosis and establishing a successful treatment plan for the patients. Detection and management of oral cancer at an early stage significantly improves the prognosis and reduced the risks of significant morbidity and mortality to the patients (Macey et al., 2015). Tumours are staged using the TNM system, in which T represents the primary tumour size, N is the status of regional lymph nodes involvement and M indicates the presence of distant metastases (Ogden, 2015). The complete TNM staging of Oral

Cancer based on American Joint Committee on Cancer (AJCC) Manual for Staging of Cancer (8th ed., 2010) (Amin et al., 2017) is presented in Table 2.2.

Complete head and neck examination and palpation are fundamental for diagnosis of oral cancer. When a suspicious lesion is identified, a biopsy needs to be done to check the status of the lesion. Conventional scalpel biopsy and histological assessment remains the most accurate diagnostic test for detection of potentially malignant disorders and oral cancer as compared to non-invasive technique such as vital staining (toluidine blue), oral cytology, and light-based detection (Neville & Day, 2002; Macey et al., 2015; Carreras-Torras & Gay-Escoda, 2015).

Several histological features such as the degree of keratinisation, nuclear pleomorphism, cellular atypia and mitotic activity are used to classify the grade of oral cancer. They are divided into well, moderate and poorly differentiated lesions. Complete histological assessment should include some other prognostic factors such as tumour thickness, an extra-capsular spread of nodal metastases and pattern of invasion (Scottish Intercollegiate Guidelines Network, 2006; Kerawala et al., 2016).

If the histopathology confirms the presence of cancerous cells, imaging technique such as Computed Tomography (CT) scans and Magnetic Resonance Imaging (MRI) are routinely used to determine the extent of the primary tumour, invasion, regional lymph nodes status and distant metastases disease (Pigadas & Jevon, 2014; Lester & Yang, 2015). Both techniques have been found to have equal specificity (false-positive 0%) however, MRI has been found to be more sensitive (false-negative 6% compared to 28% for CT). Bone involvement in oral cancer is also considered as an important indicator in treatment planning certainly for primary surgery. Standard plain radiographs such as the Orthopantomogram (OPG) are reasonably sensitive in detecting

mandibular infiltration, but this should be confirmed in doubtful cases using CT or MRI (Brown & Langdon, 1995; Frederick et al., 2002).

Other scans such as Positron Emission Tomography (PET-CT) has been widely used for identification of locally advanced oral cancer, recurrent, metastases disease and neck nodes with unknown primary (Ord & Blanchaert, 2001; Scottish Intercollegiate Guidelines Network, 2006; Kelly et al., 2013; Lester & Yang, 2015). A systematic review by Sun et al., (2015) indicated that FDG-PET/CT (sensitivity: 0.84 (95% CI 0.72-0.91), (specificity: 0.96 (95% CI 0.95-0.97) has better diagnostic performance for detection of regional nodal metastasis in primary head and neck cancer patients as compared with the CT (sensitivity: 0.63 (95% CI 0.53-0.72), specificity: 0.96 (95% CI 0.95-0.97). However, this facility is not widely available in Malaysia, of which only two health centres under the Ministry of Health Malaysia are providing the PET-CT service including Hospital Putrajaya and Hospital Pulau Pinang.

To exclude synchronous tumours or distant metastases, inspection of the upper aerodigestive tract by the ear, nose and throat specialist using chest imaging or endoscopy are advisable for patients undergoing primary diagnosis of oral cancer (Neville & Day, 2002; Lester & Yang, 2015; National Comprehensive Cancer Network, 2016). The incidence of synchronous metastases is 4% to 33% depending on the size of the tumour. It frequently presented in stage T3 and T4 and in patients with node involvement (Wolff et al., 2012).

Table 2.2: TNM Staging of Oral Cancer

Primary Tumour (T)	
TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1	Tumour 2 cm or less in greatest dimension, 5 mm or less depth of invasion.
T2	Tumour 2 cm or less in greatest dimension, depth of invasion of more than 5 mm but not more than 10 mm OR tumour more than 2 cm in greatest dimension but not more than 4 cm in greatest dimension, and 10 mm or less depth of invasion.
T3	Tumour more than 4 cm in greatest dimension OR any tumour with more than 10 mm depth of invasion.
T4a	Moderately advanced local disease* (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (oral cavity) Tumor invades adjacent structures (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face).
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery.
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in a single ipsilateral lymph node 3 cm or less in greatest dimension.
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension.
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension.
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
N3	Metastasis in a lymph node more than 6 cm in greatest dimension.
Distant Metastasis (M)	
M0	M0 No distant metastasis.
M1	M1 Distant metastasis.
Histologic Grade (G)	
Gx	The grade cannot be assessed.
G1	Well differentiated.
G2	Moderately differentiated.
G3	Poorly differentiated.
Anatomic Stage/Prognostic Groups	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1 N1 M0
	T2 N1 M0
	T3 N1 M0
Stage IVA	T4a N0 M0
	T4a N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
	T4a N2 M0
Stage IVB	Any T N3 M0
	T4b Any N M0
Stage IVC	Any T Any N M1

b. Assessment of Cervical Lymph Nodes

The involvement of cervical lymph nodes is important to be assessed in the pre-treatment staging as it is one of the predictive factors of the treatment outcome (Shaha et al., 1984). In oral cancer, stepwise metastases through the lymphatic channel usually occur, with the involvement of the first level nodes before it spreads to the lower level of lymph nodes (McKelvie, 1976). The survival rate dropped significantly when metastases involved lymph nodes in the lower region (Viviano et al., 2013).

As compared to CT, MRI and FDG-PET/CT, Ultrasound-guided Fine-needle Aspiration Cytology (FNAC) is the most accurate method for determining any lymph node involvement. The sensitivity reported in the literature is around 90% and the specificity is 100%. Open biopsy of neck lumps is usually avoided because this method has been reported to have lower survival rate due to the possibility of a lesion to spread when it is not accompanied by a simultaneous neck dissection (Brown & Langdon, 1995; Souren et al., 2016).

Sentinel lymph node (SLN) biopsy is indicated for small (T1 and T2) cancers since a negative sentinel node biopsy can avoid the morbidity due to neck dissection (Govers et al., 2013; Arya et al., 2014). SLN biopsy is also indicated following the resection of a primary biopsy for identification of any occult cervical metastases (National Comprehensive Cancer Network, 2016). However, its usefulness in Malaysia is still lacking in view of the fact that more than 50% of oral cancer diagnosed are at a late stage (Manan et al., 2016).

c. Treatment

Generally, decision making on the treatment of oral cancer should focus on the likelihood of cure as well as the quality of life of patients (physical health, social, psychological and emotional). There is no single, reliable treatment that can be used for all types of cancer. The options of treatments are variable and depend on several factors such as tumour factors, patient factors and physician factors. Tumour factors that influenced the choice of treatment are mainly based on the stage and location of the primary tumour, bone involvement, lymph nodes status, previous treatment and histology (type, grade, and depth of invasion). Patient factors including patient's age, medical condition, tolerance of treatment and compliance by patients, lifestyle and socio-economic status are also important to be considered for a successful treatment plan. Finally, physician factors include the availability of expertise and support services from various disciplines, and technical capabilities that contribute to successful treatment outcomes (Brown & Langdon, 1995; Ord & Blanchaert, 2001; Shah & Gil, 2009).

Currently, the main treatment modalities for oral cancer are surgery, radiotherapy, and chemotherapy. Early stage cases (I and II) are treated with a single modality either surgery or radiation therapy. In advanced disease, a combination of surgical resection with other adjuvant treatment such as radiotherapy (RT) and/or chemotherapy (CRT) may provide the best chance of cure although it may increase the side effects and morbidity to the patients. Despite aggressive primary treatment, locoregional recurrence accounts for approximately 80% of the treatment failure. Locoregional recurrence may be treated with surgery or re-irradiation or palliative care with or without chemotherapy based on tumour and patients' condition (Silverman, 2003; D'cruz et al., 2013).

Surgery

Surgery remains the most established mode of initial definitive treatment for a majority of oral cancers. Generally, the aim of surgical resection is to remove the whole cancerous tissues with an adequate margin to allow removal of surrounding microscopic invasion but preserving as much functionality as possible (South West Cancer Intelligence Service, 2005). Conventional surgery, laser surgery, thermal surgery and photodynamic therapy are different approaches available for surgery. Laser surgery, thermal surgery, and photodynamic therapy are indicated for small and superficial lesions while conventional surgery is preferred for advanced stage oral cancer (Kerawala et al., 2016). Reconstructive surgery following the surgical resection is indicated for patients with a functional or aesthetic loss in order to improve the quality of life of the patients (Wolff et al., 2012).

Generally, the surgical treatment outcomes depend heavily on the stage of the disease at the time of patient presentation. A retrospective study of early squamous carcinoma (T1, T2, and T3) of the buccal mucosa treated with perioral wide excision reported that of 147 patients, only 39(26.5%) presented with complication (local recurrence, locoregional recurrence and neck node metastases) during follow-up of the post-surgery. Poor differentiation on histologic analysis was the significant prognostic determinant for recurrence. Three-year survival rate and disease-free survival rate for this study group were high at 91% and 77% respectively (Ganpathi Iyer et al., 2004). Generally, this finding revealed that early diagnosis and implementation of appropriate surgical treatment and post-operative therapy have all contributed to improved outcomes and survival of patients with oral cancer (Shah & Gil, 2009).

Management of the Neck Lymph Nodes

Management of the neck lymph nodes should follow the same treatment principles as those applied for the primary tumour. If surgery is the preferred treatment for the primary tumour, the neck should also then be approached surgically. In N0 neck disease, plain observation is indicated after therapy (National Comprehensive Cancer Network, 2016). However, elective neck dissection should be offered to all patients including those with clinically normal lymph-node status (cN0) because occult metastases to the cervical lymph nodes occurred in 20% to 40% of the oral cancers (Wolff et al., 2012). In the case of node positive involvement (cN+), the appropriate lymphadenectomy, usually elective neck dissection or modified radical neck dissection should be carried out (National Comprehensive Cancer Network, 2016). Recent evidence suggested that cervical lymphadenectomy in the form of elective neck dissection offered improved survival and disease-free survival as compared with therapeutic neck dissection for the majority of oral cancers (Kerawala et al., 2016).

Radiotherapy

Radiotherapy may be used alone for curative intent (radical radiotherapy) or as adjuvant therapy following surgery to improve local control or concurrently with chemotherapy as clinically indicated or as palliative radiotherapy to provide symptomatic relief. Radiotherapy delivered postoperatively to selected patients at high risk of locoregional recurrence may improve locoregional control and survival outcomes (Scottish Intercollegiate Guidelines Network, 2006).

Although conventional radiotherapy plays a key role in advanced stage cancer, the outcomes remain relatively poor. Several approaches have been developed to improve

its anti-tumour efficacy such as altered fractionated radiotherapy (accelerated and hyperfractionated) and concomitant chemoradiotherapy. Both approaches showed a significant benefit on locoregional control and survival outcome as compared to conventional radiotherapy (Calais et al., 1999; Kerawala et al., 2016). The benefit on locoregional control and survival outcome in favour of altered fractionation versus conventional radiotherapy was 6.4 % and 4.3% respectively at 5 years (Mazeron et al., 2009). Meta-analysis of chemotherapy in head and neck cancer based on the collection of data of 63 randomized trials showed that the addition of chemotherapy to locoregional control resulted in survival benefit of 4% at 5 years as compared to radiotherapy alone.

The management of oral cancer continues to evolve over time in order to enhance the treatment efficiency. The introduction of new technology in cancer therapy such as the Intensity-modulated radiation therapy (IMRT: directed irradiation technique at the target site) minimizes the radiation exposure to the healthy tissue and subsequently less morbidity will be experienced by the cancer patients (Ord & Blanchaert, 2001). However, access to this treatment modality is limited to the healthcare facilities across the Asia-Pacific region including Malaysia (D'cruz et al., 2013).

Chemotherapy

Chemotherapy is indicated for advanced stage of oral cancer in order to destroy or slow the growth of cancer cells by using a specific drug. Chemotherapy may be used as induction chemotherapy prior to local treatment or as palliative therapy in patients with recurrent and/or metastatic disease. However, due limited evidence of survival benefit was found when chemotherapy alone was used, chemotherapy is usually administered

concurrently with radiotherapy. Commonly used agents include cisplatin, carboplatin, 5-fluorouracil, paclitaxel and docetaxel (Zhang et al., 2015; Marta et al., 2015).

The use of concurrent chemotherapy to radiation therapy has been shown to increase the survival rates in patients with head and neck cancer as compared to neoadjuvant chemotherapy and adjuvant chemotherapy after radiation therapy. Data from two meta-analyses, showed that the addition of concurrent chemotherapy to radical radiotherapy for treatment of patients with locally advanced oral cavity cancer resulted in 17% reduction in the risk of death (Scottish Intercollegiate Guidelines Network, 2006). Concurrent chemoradiotherapy should only be administered where there are appropriate facilities for monitoring toxicity because chemotherapy when added to definitive treatment resulting in an increase in toxicity (El-Sayed & Nelson, 1996; Fu, 1997).

Targeted Therapy and Immunotherapy

Discovery in molecular biology has provided a deeper understanding of the development of carcinomas. This provides hope that the targeted therapies will be possible in the future, thus facilitating health care providers to predict tumour behaviour and select the most appropriate treatment for a patient. The use of a molecular marker in the pre-malignant lesions will provide a clinician with specific diagnostic and preventive strategies (Ord & Blanchaert, 2001). However, only a few trials have been conducted regarding the therapy in head and neck cancer. The evidence is still insufficient to determine whether the emerging therapies (targeted therapy and immunotherapy) may have advantaged patients outcomes (Airoldi et al., 2001; Chan et al., 2015).

d. Follow-up Care

The treatment for oral cancers often results in acute and chronic disruptions to oral health and functioning (Pateman et al., 2015). The surgical procedure may result in patient having negative impacts such as pain, disfigurement, speech and swallowing difficulty, disrupted social activity, and reduced mouth opening. The additional side effects such as xerostomia, dysphagia, osteoradionecrosis and altered taste caused by toxicities of treatment involving radiotherapy and/or chemotherapy resulting in a higher burden of oral morbidity and impact the quality of life of the patients (Gotay & Muraoka, 1998; Mehanna & Morton, 2006; Chen et al., 2013; Shavi et al., 2015).

As the population of head and neck cancer survivors increased, it has become evidently important for healthcare providers to have appropriate skills in managing complication of therapy experienced by the patients. The manifestation of oral complications may start immediately or years after the completion of treatment. Swallowing and speech difficulty, and dry mouth (xerostomia) are the most common side effects associated with both surgery and radiation therapy. Patients with xerostomia are at high risk for dental caries and thus require aggressive oral hygiene regimens and routine dental surveillance (Andrews & Griffiths, 2001; Epstein et al., 2001).

Swallowing abnormalities, xerostomia, and poor dentition may result in nutritional deficiencies. There is growing evidence to support dietary alteration and therapeutic swallowing exercise for maintenance of swallowing function before, during and/or immediately after cancer treatment (Murphy & Deng, 2015). However, the effectiveness remains uncertain with the conflicting lack of high-quality studies for meaningful assessment of the therapy. It was suggested that swallowing rehabilitation remains as

the current management option for dysphagia for oral cancer patients (Riffat et al., 2015; Perry et al., 2016).

The impact of cancer treatment highlights the need for total and holistic care for cancer patients. Qualitative research has provided greater insight into the need for support services related to oral health and psychosocial wellbeing for cancer patients (Riffat et al., 2015). The effective pre-treatment assessment of the oral health condition and close follow-up of the patient helps in ensuring the patient's ability to function normally in terms of her physical, mental and social being (Moore et al., 2014).

Recommendations for follow-up care are often limited by a lack of adequately powered trials exploring the efficacy of supportive care interventions. That being said, clinician depends on their experience to identify the types of problems that patients encounter and the supportive care appropriate for each patient. Supportive care includes a wide array of disciplines, including general dentistry, oral surgery, prosthodontics, speech and language therapy, physical therapy, nursing care, nutrition, and dietetics. In order to provide adequate supportive care for cancer patients, a dedicated team should include the dentist and various allied health professionals such as nurses, speech and swallowing therapist, nutritionist and psychosocial workers to address the complex needs of these patients (Neville & Day, 2002; Scottish Intercollegiate Guidelines Network, 2006; Murphy & Gilbert, 2011; Belgian Health Care Knowledge Centre, 2014a; National Comprehensive Cancer Network, 2016).

2.2 The Approaches to Evidence-based Practice

2.2.1 Introduction

Evidence-based practice (EBP) has increasingly been accepted as the standard for many health care disciplines including medicine and dentistry in the 1990s. It has been defined as “integrating individual clinical expertise with the best available external scientific evidence from systematic search” (Sackett, 1997). American Dental Association (2017) defined EBP as “an approach to health care that requires an integration of systematic assessment of relevant scientific evidence with clinician’s expertise and patients’ treatment need and preference in deciding the best care for patients”.

EBP has changed the way healthcare has been delivered. In EBP, clinicians are relying more on the best available scientific evidence rather than their past clinical experience in making clinical decision (Bader & Shugars, 1995). EBP is necessary because knowledge acquired during training becomes fast out of date as new information and technology emerges. It is important for the clinicians to keep abreast with the developments in diagnosis, prevention and treatment, and emerging causes of disease for the sake of patients’ safety (Hackshaw et al., 2006). Furthermore, expanding the scientific basis for clinical care will protect healthcare professionals from legal liability by fully disclosing all information that has been critically reviewed (Ismail & Bader, 2004). Moreover, EBP encourages the clinicians to make use of the overwhelming evidence available by translating them into their daily practice (Richards & Lawrence, 1995).

2.2.2 What Constitutes Evidence?

Best care demands the best research evidence with the least bias in terms of design, analysis, and interpretation of the data (Ismail & Bader, 2004). Based on Daly et al. (2007), the highest level of the evidence is the strong evidence from at least one systematic review of multiple well-designed randomised controlled trials. The type and the hierarchy in the assessment of the strength of evidence are illustrated in Figure 2.1.

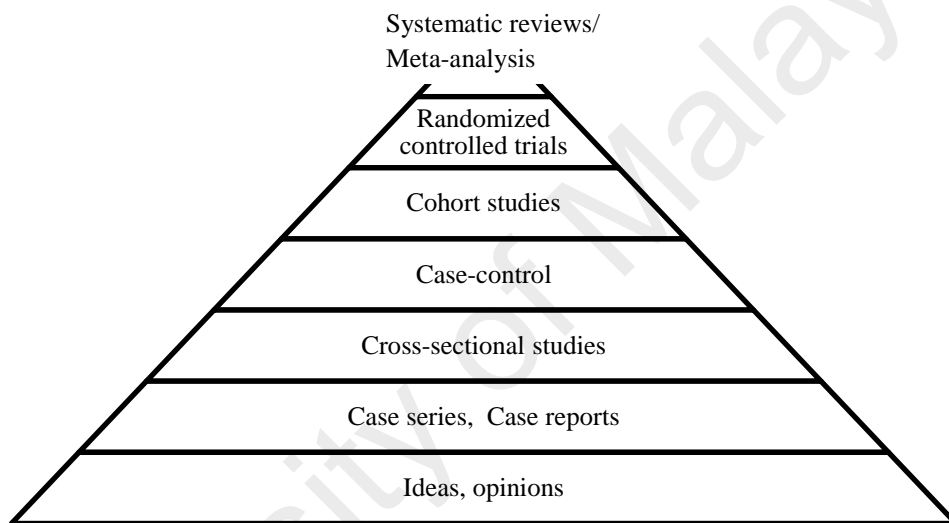


Figure 2.1: Hierarchy of evidence (Daly et al., 2007)

There are several basic sources of evidence namely: seeking expert opinion, textbook and electronic database. Searching for the evidence from an electronic database would be the best way because it is more comprehensive and up to date (Richards & Lawrence, 1995; Heneghan & Badenoch, 2013). Cochrane Library produced by the Cochrane Collaboration, MEDLINE and EMBASE are among the major databases of clinical research (McKibbin, 1998). About 10,000 new randomised controlled trials are included in the MEDLINE every year (Grol & Grimshaw, 2003) and more than 400,000 trials have been identified by the Cochrane Collaboration (Haines et al., 2004). The appearance of the evidence-based journals such as Evidence-Based Dentistry and The

Journal of Evidence-Based Dental Practice has facilitated clinicians to access the research evidence (Sackett et al., 1996; Ismail & Bader, 2004).

Systematic reviews are the cornerstone of EBP (Higgins & Green, 2008). As clinicians need new skills and time to examine the overwhelming number of primary research, most of them are relying on the systematic reviews that are clinically relevant and available to them (Grol & Grimshaw, 2003). The Cochrane Collaboration and The NHS Centre for Review and Dissemination are two websites which are very useful to look for systematic reviews regarding the effect of healthcare (Daly et al., 2007). However, the number of systematic reviews for certain clinical areas including dentistry are limited and clinicians still need to depend on the primary studies to obtain good quality evidence in making a clinical decision (Kao, 2006).

2.2.3 The Process of Translating Evidence into Practice

Shifting to EBP would benefit all healthcare professionals as well as the patients. The aim of EBP is to help healthcare professionals to provide the best care for their patients (Kao, 2006). It has been reported in previous studies that adherence to evidence-based practice has the potential to improve the quality of healthcare (Brasca et al., 1986; French et al., 1989; Santoso, 1996).

Many organisations worldwide had given support in promoting EBP. For example, Cancer Care Ontario had initiated their Program in Evidence-Based Care (PEBC) since 1997 (Browman, 2012) and American Dental Association had developed the Center for Evidence-Based Dentistry in order to promote evidence-based practice by disseminating the best available scientific evidence for dental practitioners (American Dental Association, 2017).

Effective EBP requires several steps namely formulating the question that is relates to the identified clinical problem followed by tracking down the necessary information to answer the question (McKibbon, 1998; Goldstein, 2002). It is important for a clinician to systematically extract useful information and critically evaluate the validity of the research evidence using a specific methodology before assimilating it into decision making (McKibbon, 1998; Goldstein, 2002; Clarkson et al., 2003; Faggion & Tu, 2007). The critical question for a clinician to take into account when making a clinical decision is whether the application of the research evidence will improve the health care of the patients they are treating. Finally, evaluation of the process needs to be carried out to ascertain if optimal outcomes have been achieved for the patients (McKibbon, 1998; Goldstein, 2002).

The process of dissemination and implementation of the evidence is crucial for the success of EBP (Clarkson et al., 2003). It was found that profession-orientated interventions such as educational activities, reminders, audit and feedback on performance are effective for the implementation of research evidence in practice. However, the effects are varied depending on the health activity and targeted behaviour, for example, outreach educational visits were found to be useful for influencing prescribing activities and the reminder was useful for preventive activities (Grol & Grimshaw, 2003). Kitson et al., (1998) outlined three core elements that may influence the successful implementation of research findings into practice namely: the level of the evidence, the context into which the research finding is to be implemented and the method of facilitating the change. It was suggested that most successful implementation would seem to occur when the level of evidence is high, the contextual condition is receptive to change and appropriate method of facilitating the change is used.

One of the main challenges in adapting EBP is that clinicians need to keep up with the rapid movement in the health-care knowledge and new emerging evidence (Grol & Grimshaw, 2003). Clinician needs to develop skills on how to go through the rigorous process of EBP particularly during undergraduate training in order to encourage its spread through the profession (Richards & Lawrence, 1995). Research evidence when used systematically has the potential to provide optimal care to the patients which are both clinically and cost effective, and delivered with proper regard to the dignity of the patients (Clarkson et al., 2003; Kao, 2006).

The process of translating the finding of systematic reviews to a format that clinicians can readily use such as clinical practice guidelines (CPGs) may help clinicians to adopt EBP (Sackett et al., 1996; Grol & Grimshaw, 2003). By translating the best available scientific evidence into specific recommendations, a guideline can be a useful tool to inform clinicians and patients the best option for health care (Burgers et al., 2003a). For busy clinicians, incorporating the recommendation of well-developed CPGs into daily practice can be the efficient way to ensure their practice is in line with the current and standard of health care (Green & Piehl, 2003). The importance of evidence-based practice guidelines and how it is incorporated in clinical practice including cancer management is discussed in the following section.

2.2.4 Evidence-based Practice Guideline

The use of clinical practice guidelines (CPGs) is assuming a growing importance with the increasing moves in evidence-based practice (Pagliari & Grimshaw, 2002). The Institute of Medicine in the United State of America defined CPGs as ‘systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical conditions’ (Field & Lohr, 1990). With the growth of the

evidence-based practice, the development of CPGs has moved from expert consensus towards evidence-based methodology (Lugtenberg et al., 2009).

Worldwide, a number of government agencies, professional bodies and guideline networks such as The Agency for Healthcare Research and Quality (The Agency For Healthcare Research and Quality, 2016), the American Dental Association (American Dental Association, 2017) and Scottish Intercollegiate Action Group (Scottish Intercollegiate Guidelines Network, 2015) have been actively involved in the development and publication of CPGs. As a result, there has been a rapid expansion in the number of CPGs over the past two decades. A wide variety of CPGs are easily accessible through practice guideline databases and guideline developer websites.

Guideline International Network is an international collaboration which was founded in 2002 to promote systematic development and application of CPGs. The Guideline International Network provides regularly updated international guidelines for the clinicians to use in clinical areas of interest (Ollenschläger et al., 2004). In addition, the French National Federation of Cancer Centers (FNLC) (Fervers et al., 2001), Cancer Care Ontario (Browman, 2012) and National Comprehensive Cancer Network (NCCN) are among organisations that are actively involved in the development and updating of evidence-based guidelines for cancer management. For example, the NCCN has produced more than 50 oncology guidelines on the full continuum of cancer care from the point of diagnosis to the follow-up care (Irwin & Peppercorn, 2012).

The growing importance of CPGs has been recognized by the Ministry of Health Malaysia. Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAs) is responsible for the development, approval, and implementation of local CPGs. Besides MaHTAs, CPGs are also developed by professional societies and the

Oral Health Division. A substantial number of multidiscipline CPGs have been developed over the past decade to promote standards for health care and by keeping abreast with the growing emphasis of EBP. This includes the development of several guidelines on cancer management involving Nasopharyngeal Carcinoma, Cervical Cancer, Breast Cancer, Colorectal Carcinoma and Primary Prevention and Early Detection of Pre-cancerous and Oral Cancer. (Ministry of Health Malaysia, 2002; Ministry of Health Malaysia, 2015).

The most important benefit of CPGs is their potential to improve both the quality of care and patients health outcomes. A large number of health care provider have started adapting CPGs since the 1990s (Cheah, 1998). A number of studies have been carried out to evaluate the impact of CPGs on clinical practice. A systematic review that was conducted to assess the effectiveness of CPGs in a variety of healthcare setting reported a significant improvement in 89% of the 91 studies that measured the effect on the process of care and 70% of 17 studies that measured patient health outcomes (Grimshaw et al., 1995b). A more recent systematic review that assessed the effect of Dutch evidence-based guidelines indicated similar findings with significant improvement in both process of care and patient outcomes (Lugtenberg et al., 2009).

Cancer care has also reaped the benefit from the implementation of evidence-based guidelines (Grimshaw et al., 1995b; Graham et al., 2002). Previous studies that evaluated the impact of CPGs on oncology treatment revealed that improvements have been demonstrated in compliance with evidence-based guidelines in terms of reduction in length of hospital stay and health care cost (Smith & Hillner, 2001), benefit for quality and safety of patients' care (Patkar et al., 2006) and reduction in diagnostic interval (duration from first presented symptoms to date of diagnosis) (Neal et al., 2014).

A study by a regional cancer network in France reported that the introduction of the CPGs with appropriate implementation strategy resulted in a significant change in the compliance rate with the guidelines for the assessable overall treatment sequences (surgery, radiotherapy, chemotherapy and hormonal therapy with initial examination and follow-up if they were performed in the participating hospital). The number of individual medical decisions complying with the CPGs were also increased through their cancer network (Ray-Coquard et al., 2002).

The successful introduction of a guideline depends on the methods used in the development as well the strategy used for dissemination and implementation of the guidelines (Cheah, 1998). Generally, valid CPG requires rigorous evidence-based development methodology in combination with expert judgment and patients' need and preferences (Green & Piehl, 2003; Linskey, 2010).

Previous studies suggested that CPGs with a simple format, addresses an acute condition, supported with good quality of evidence, and compatible with the existing health system were most likely to be followed (Grilli & Lomas, 1994; Grol et al., 1998; Foy et al., 2002; Burgers et al., 2003b). Grimshaw et al. (1995b) suggested that CPGs were more likely to change practice if they were developed by local groups including representatives of key disciplines, disseminated by specific educational interventions and implemented with reminders during the consultation. Guideline providing algorithm for certain clinical circumstances may facilitate its use by clinicians (Irwin & Peppercorn, 2012). The description of the guideline development concepts and the processes involved are discussed in detail in the following section.

2.3 Development of Best Practice Guidelines

2.3.1 Developing Valid Best Practice Guidelines

CPGs are considered to be very important in providing information about therapeutic approaches to the clinicians. Therefore, it is imperative that the CPGs are developed using a rigorous process of translating the scientific evidence into valid recommendations. Generally, the validity of CPGs is related to three main factors namely: 1) the composition of the development group, 2) the method of identification and synthesis of the evidence and 3) method of formulating recommendations. CPGs are more likely to be valid if they are developed by national or regional development group (with the representative of an expert in their field), using systematic reviews in identification and extraction of the evidence with an explicit link between recommendation and the supporting evidence (Faggion, 2013; Attia, 2013).

2.3.2 The Concepts Guideline Development

Advances towards an evidence-based development of CPGs have undoubtedly improved the quality of the CPGs disseminated to health professionals (Cluzeau et al., 1999). Generally, there are two concepts of guideline development available namely: 1) the “De Novo” development through a systematic appraisal of available evidence and 2) guideline adaptation which is a systematic approach for customizing the existing guideline(s) by adopting or adapting the recommendations for application in the local context (Graham et al., 2002; Graham et al., 2005). The choice of approach to be used mainly depends on the local circumstances, the availability of evidence and resources at the time of guideline development. The detailed process involved in each concept of guideline development is documented as follows:

2.3.2.1 The *De Novo* Development

The de novo guideline development involves several steps as follows: 1) topic selection, 2) formation of guideline development group, 3) search for evidence, 4) critical appraisal of the evidence, 5) synthesis of the evidence, 6) formulation of the recommendations and finally 7) consultation and peer review (Woolf, 2000; Fervers et al., 2001; Wollersheim et al., 2005; Faggion, 2013; Scottish Intercollegiate Guidelines Network, 2015; Yoshida et al., 2015). Systematic reviews are often used as a starting point for developing CPGs. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology developed by an international group of researchers in 2009 can be used as a basis for some aspects of guideline development particularly in the first five steps as aforementioned. The PRISMA statement that consists a 27-items checklist may also be useful for critical appraisal of systematic reviews (Moher et al., 2009). The detail description of each step is discussed in the following sections:

1) Topic Selection

In most programmes, organisations which coordinate the guideline development are responsible for selection of the guideline topic. In some cases, the topic can be proposed by the policymakers or health authorities (Burgers et al., 2003a). In Malaysia, the topic of CPGs is determined by the CPG Technical Advisory Committee (TAC), MaHTAS, professional societies or the Oral Health Division, Ministry of Health Malaysia (Ministry of Health Malaysia, 2015). The SIGN outlined several criteria that can be used in prioritising topics for guideline development as follows: burden of the disease, the existence of inconsistency in practice, clinical priority, the perceived need by the relevant stakeholders which have the potential to improve health outcome (Scottish Intercollegiate Guidelines Network, 2015).

2) Formation of Guideline Development Group

The composition of guideline development group should be multidisciplinary including clinical and methodological experts with the representative of patients where possible. The size can vary between the guideline development group (Burgers et al., 2003a).

3) Search for Evidence

The definition of a specific clinical question including the population, intervention, comparison and outcome forms the basis of the literature search. The identification, compilation, and selection of evidence should be carried out according to a specific methodology to ensure that all relevant evidence has been gathered.

4) Critical Appraisal of the Evidence

Explicit analytical criteria need to be used to determine the methodological quality and validity of the research findings. Studies are assigned a level of evidence to reflect the hierarchy of evidence quality. Many appraisal instruments are available to grade the quality of the evidence (Elwood, 2007). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system is one of the comprehensive approaches to assess the overall quality of evidence and grading of the recommendations and have been adopted by many organisations worldwide (Guyatt et al., 2008; Vandvik et al., 2013).

5) Synthesis of the Evidence

The relevant information from the selected evidence are summarized and tabulated in an evidence table. This facilitates a comparison of the various interventions and serves as a basis for the formulation of a recommendation. Meta-analysis can be carried out to pool data of multiples studies, when appropriate.

6) Formulation of the Recommendations

Recommendation is formulated based on the synthesis of the evidence. Several factors need to be taken into account for the development and grading of a recommendation as follows: 1) the quality of evidence, 2) balance between effectiveness of the treatment and side effects, 3) patients' needs and preference and 4) cost of the treatment. Fervers et al., (2001) in their SOR guideline development project defined 'standards' and 'options' as best practice agreed by the majority of a multidisciplinary group whereas 'recommendations' refer to additional information that assist clinicians to choose the appropriate option. The methods used to achieve consensus (formal or informal) and grading of recommendation may vary between guideline development groups.

7) Peer Review and Consultation

The feedback and agreement are obtained from the independent reviewers (content experts, targeted users or relevant stakeholders) regarding the guideline in a draft form before the final guideline is formulated.

2.3.2.2 Guideline Adaptation Concept

As the development of new evidence-based best practice guidelines would involve a rigorous process and requires a lot of time and resources, the guideline adaptation concept using a validated framework provides a possible alternative to the *de novo* development through local adaptation of high quality existing guidelines (Fervers et al., 2006). Adaptation of guidelines can be considered in selected circumstances when one or more quality guidelines from other organizations already exist on the similar topic (Chakraborty et al., 2014).

Guideline adaptation follows similar procedures used in the *de novo* guideline development with some modification in certain steps. Two approaches have been identified which are partly overlapping. The Practice Guideline Evaluation and Adaptation Cycle (PGEAC) (Graham et al., 2003) and the ADAPTE (The Adapte Collaboration, 2009) illustrate a systematic way to evaluate guideline quality and validity by comparing different guidelines recommendations on the same topic (Groot et al., 2008). Both approaches are further discussed in detail in the following section.

a. The Practice Guideline Evaluation and Adaptation Cycle (PGEAC)

The Practice Guideline Evaluation and Adaptation Cycle (PGEAC) was developed for a project that involved creating a CPG for National Leg Ulcer Community Care in Ottawa, Ontario in order to optimise use of resources in the development process (Graham et al., 2005). It is a ten steps approach as illustrated in Figure 2.2 that was used to guide the process of whether to adopts one guideline as it is, or adopts the guideline but omit certain recommendations or accept certain recommendations from several guidelines and adapt them the into new local guidelines.

This approach has been used by a number of guideline programmes in Canada, for example, the Registered Nurses Association of Ontario (MacLeod et al., 2002), the Society of Gynecologic Oncologist of Canada (Elit et al., 2006) and The Canadian Strategy for Cancer Control (Syme et al., 2006). The PGEAC was validated by a study of pre and post-implementation of the community leg ulcer care guideline as aforementioned. The study found that the healing rate was significantly increased from 23% to 59% following implementation of the practice guideline (Harrison et al., 2005).

b. The ADAPTE

This approach has been developed by the international working group the ADAPTE Collaboration involving the French National Federation of Comprehensive Cancer Centre (FNLCC) and the Department of Cancer Control of the Quebec Ministry of Health and Social Services. It consists of 24 steps (Figure 2.3) that were initially used in adapting the cancer guideline that was developed in France for cancer care in Quebec. It is supported by a manual and resource toolkit that can be accessed through The ADAPTE Collaboration websites (The Adapte Collaboration, 2009). This framework has been used by certain organizations such as the American Society of Clinical Oncology (Bower et al., 2014) and Canadian Thoracic Society (Gupta et al., 2009) in their guideline programmes.

The first evaluation of ADAPTE process on a group of physicians, pharmacists, nurses and allied health professional reported that most of the respondents judged the adaptation process and the manual as being clear and comprehensive, and expected benefits from using the ADAPTE process. However, some respondents commented that the lack of appropriate source guidelines and the complexity of the ADAPTE framework were the main difficulties of using the ADAPTE process (Fervers et al., 2011). Therefore, more expertise and time were needed throughout the process (Chakraborty et al., 2014).

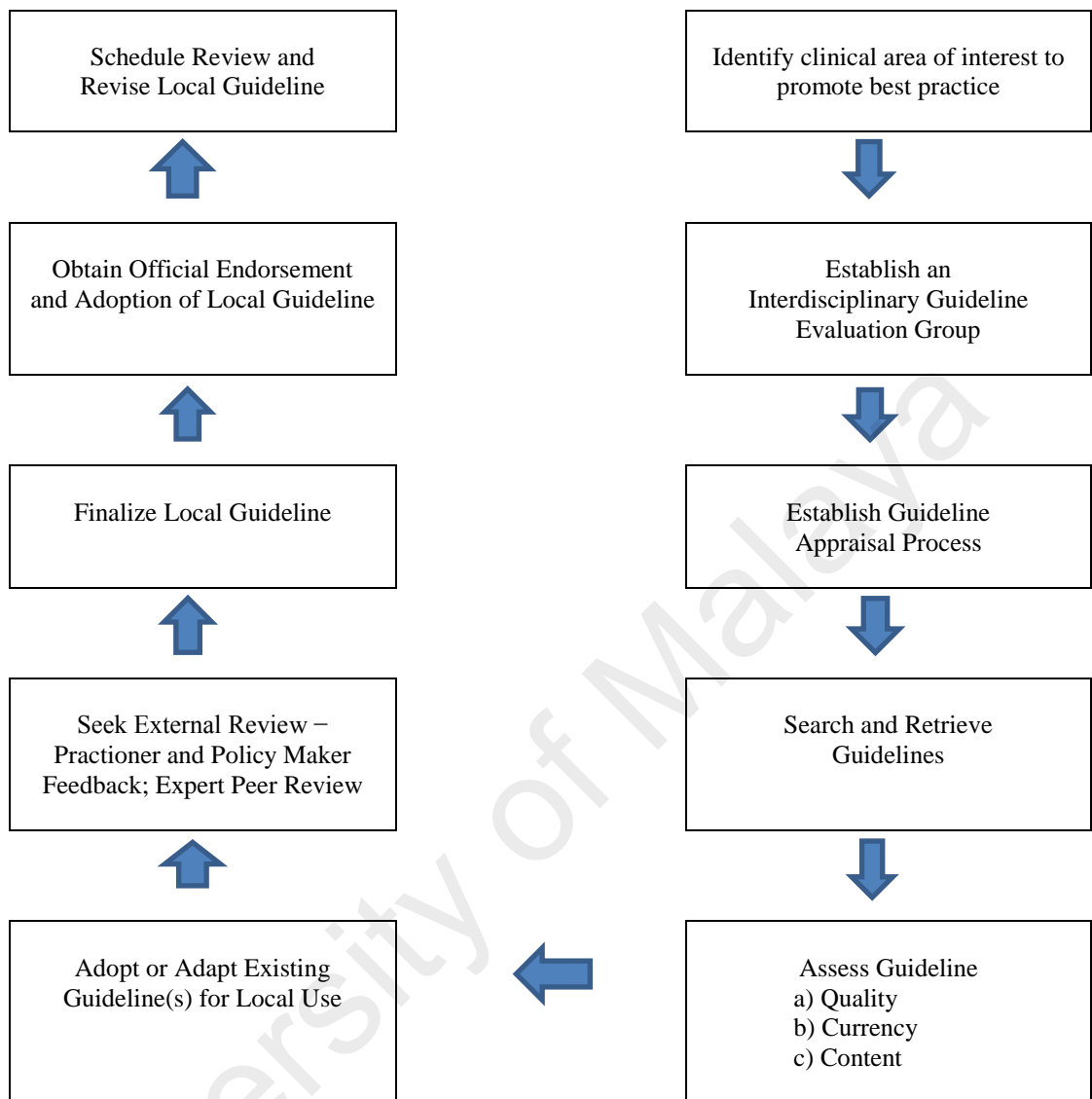


Figure 2.2: The Practice Guideline Evaluation and Adaptation Cycle (PGEAC)
(Graham et al., 2002; Graham et al., 2003)

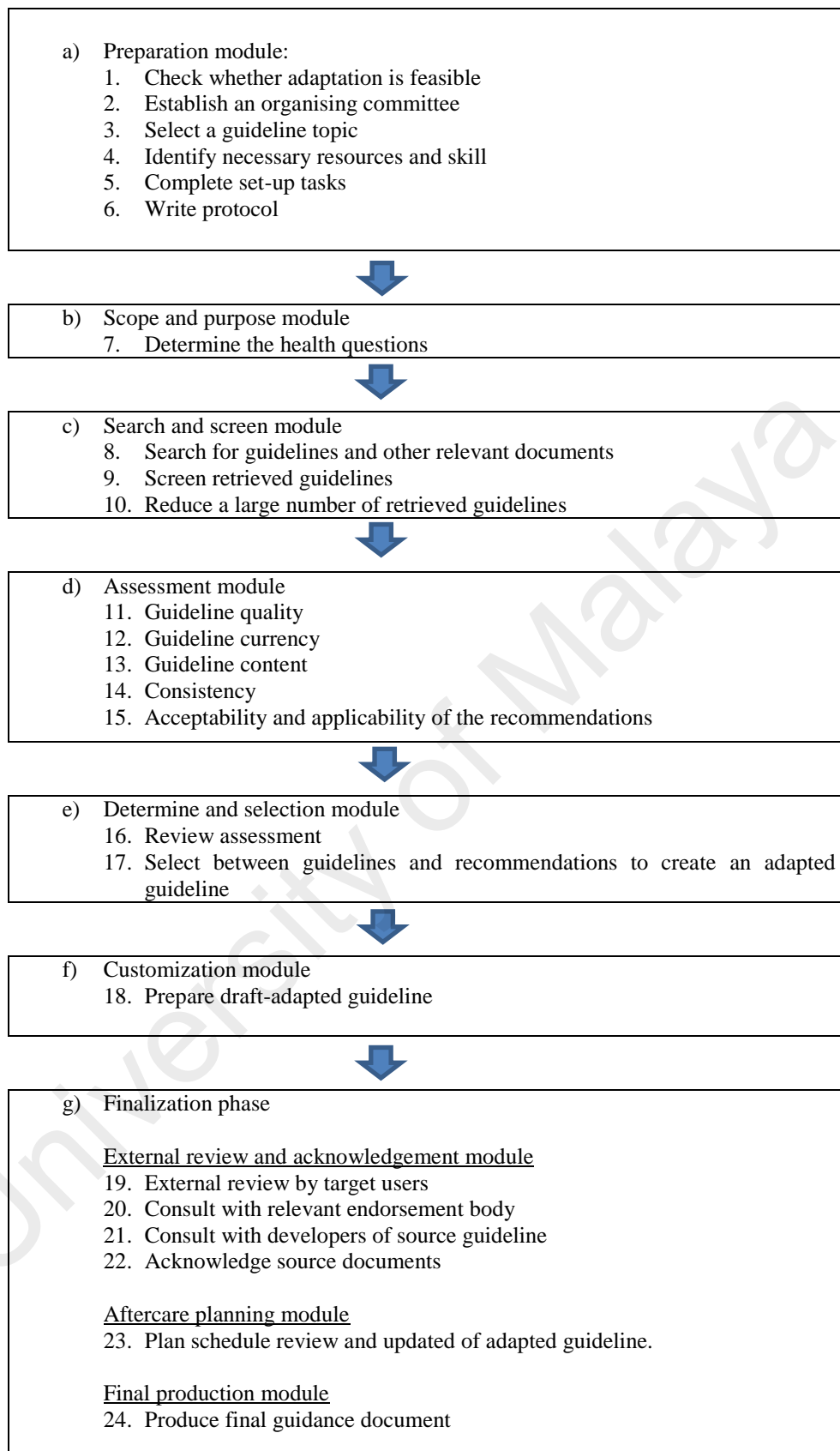


Figure 2.3: The ADAPTE process (The Adapte Collaboration, 2009)

2.4 Quality Assessment of Best Practice Guidelines (BPGs)

2.4.1 Introduction

The introduction of BPGs had shown an improvement in the process of care and outcome of patients. However, there is a considerable range in the size of the improvements between the guidelines. Generally, the benefits of a BPG are only as good as the quality of the CPG themselves (Grimshaw et al., 1995a; Grimshaw et al., 2004a; The AGREE Next Steps Consortium, 2009). The Appraisal of Guidelines for Research and Evaluation (AGREE) Collaboration defined guideline quality as the confidence that potential biases inherent in guideline development have been addressed adequately and that the recommendations are both internally and externally valid, as well as feasible for practice (The AGREE Collaboration, 2003).

Several initiatives have been established by guideline programmes worldwide to ensure that their guidelines meet the highest international standard. Many organisations such as World Health Organization (WHO) (World Health Organization, 2012), Scottish Intercollegiate Guidelines Network (Scottish Intercollegiate Guidelines Network, 2015), Clinical Guidelines Network Cancer Council Australia (Clinical Guidelines Network Cancer Council Australia, 2014), National Institute for Health and Clinical Excellence (National National Institute for Health and Clinical Excellence, 2017) and the French National Federation of Cancer Centers (Fervers et al., 2001) have published standard methodology for their guideline developers. In addition, the WHO established the Guideline Review Committee to monitor the quality of guidelines developed under their programme (World Health Organization, 2016).

In Malaysia, the Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAs) conducts training on the development of evidence-based guidelines and had published a standard for guideline methodology in order to control the quality of guidelines produced in this country. All guidelines need to be approved by Health Technology Assessment and Clinical Guidelines Councils, Ministry of Health Malaysia before dissemination to the relevant groups (Ministry of Health Malaysia, 2015).

Certain organizations such The Agency for Healthcare Research and Quality (AHRQ, formerly known as US Agency for Health Care Policy and Research (AHCPR), and Cancer Guidelines Action Group (Canadian Partnership Against Cancer) have developed guideline databases namely National Guideline Clearinghouse (The Agency For Healthcare Research and Quality, 2016) and Guidelines Resource Centre: SAGE Directory of Cancer Guidelines respectively (Cancer Guideline Action Group, 2016). Beside full-text guidelines, the websites also contain information on the standard methodology as an effort to emphasize the need for certain criteria to be fulfilled by the guidelines for publication.

Adherence to the standards methodology could increase the quality of the guidelines. For instance, a comparison on the quality of the US Agency for Health Care Policy and Research (AHCPR) guidelines with other North American guidelines developed subsequently after the AHCPR ended its guideline development program revealed that the AHCPR guidelines are of high quality as compared to the newer guidelines. Most of the later guidelines ($\geq 80\%$) did not perform any systematic review or use a multidisciplinary panel of experts in synthesizing the evidence. Conversely, all AHCPR

guidelines complied with these important aspects in the development process (Hasenfeld & Shekelle, 2003).

2.4.2 Why is an Appraisal of Guidelines Needed?

Given the overwhelming number of practice guidelines in the medical fields, there is increasing concern about their quality and reliability to be used in practice. Uncertainty persists on which guideline to follow or introduce in different practices, particularly when there is a proliferation of guidelines for the same clinical condition (Littlejohns et al., 1999).

Many studies have been carried out to examine the quality of multidisciplinary practice guidelines. Assessment of practice guidelines published in the late 1880s and 1990s using appraisal tools developed by Shaneyfelt et al. (1999) and Grilli et al. (2000) showed that although methods for the development of explicit evidence-based guidelines have been published, the quality of practice guidelines issued by specialty societies remained unsatisfactory. Grilli et al. (2000) evaluated 431 guidelines and found that most of the guidelines did not meet the quality criteria assessed. Sixty-seven percent gave no information on the type of stakeholders involved in the development process, 88% did not report the search strategy and 82% did not give any explicit grading of the evidence supporting the recommendations. The finding by Shaneyfelt et al. (1999) revealed that more than half (56.9%) of 279 guidelines evaluated did not adhere to the methodological standard. Although the quality of practice guidelines have been significantly improved over time for the domains assessed (ranged of improvement: 3.6% to 21.0%), the finding suggested that all aspects of guideline development still need further improvement particularly in the identification and

grading of supporting evidence (>66.0 % of noncompliance rate) (Shaneyfelt et al., 1999; Grilli et al., 2000).

Another study assessing the methodology quality of practice guidelines published between 1980 and 2007 using a validated appraisal tool (the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument) have found that the quality scores remained moderate to low over the last two decades. Beside significant improvement over time on most of the domains, the quality score for Rigour of Development Domain remained low (40%). Rigour of Development domain is considered important in determining the quality of a guideline because this domain specifically focuses on the degree to which the guideline development process was evidence based (Alonso-Coello et al., 2010).

More recent studies that used the AGREE instrument in their assessment, found a large variation in the quality of the guidelines. The mean quality score of evaluated domains ranged from as low as 20.0% for the Domain Applicability to the highest 72.0% for Domain Scope and Purpose. Domain Applicability was the most poorly addressed by the guidelines. Most of the guidelines failed to adequately consider the important issues related to the strategy used for dissemination and implementation of a guideline (Pencharz et al., 2001; Harpole et al., 2003; Pentheroudakis et al., 2008; Huang et al., 2013; Brosseau et al., 2014; Yanming et al., 2015; Yaşar et al., 2016). The successful introduction of a guideline is not depending on the developing process alone, but must be coincide with appropriate strategies for dissemination and implementation of the guideline (Grimshaw & Russell, 1993; Grol et al., 2003).

Appraisal of multidiscipline guidelines developed by the WHO using the AGREE II instrument showed that some of their guidelines are still lacking in the methodological

quality and reporting particularly in the Domains Stakeholder Involvement, Applicability and Editorial Independence. The WHO developed a substantial number of guidelines every year and their guidelines are used by most of the United Nation member countries. Therefore, it is important that their guidelines are developed using a rigorous and transparent method (Polus et al., 2012; Burda et al., 2014).

The evidence suggested that, the quality of a guideline needs to be critically evaluated by a healthcare provider before implementing any recommendation in practice (Grilli et al., 2000). This is to ensure that they are based on valid guideline recommendations as well as feasible in providing the best care possible to their patients (Marshall, 2000). Application of guidelines with questionable validity or reliability in a practice may not benefit and but also may harm the patients (Hasenfeld & Shekelle, 2003).

2.4.3 Guideline Appraisal Tools

An appraisal tool is one of the means that helps guideline users in assessing the guideline quality. In 1992, The Institute of Medicine in the United State of America had published the first appraisal instrument for used by various parties in formal evaluations of guidelines. The instrument has 46 descriptive questions related to the seven attributes: validity, clarity, multidisciplinary process, clinical flexibility, reliability and reproducibility, clinical adaptability, and scheduled review (Field & Lohr, 1992). Since then, the used of guideline appraisal tools has been well recognized all over the world (Vlayen et al., 2005).

2.4.3.1 Selection of the Guideline Appraisal Tools

Numerous tools have been developed to assess the quality of guidelines. Generally, the appraisal tools vary considerably in terms of the quality dimensions covered, rating system, and numbers of questions covered. Previous systematic reviews comparing several existing guideline appraisal tools could serve as a basis for the selection of the most appropriate tool to be used (Graham et al., 2000; Vlayen et al., 2005; Siering et al., 2013) .

Graham et al. (2000) identified thirteen guideline appraisal instruments in their study. All instruments were developed after 1992 and contained 8 to 142 questions/statements. The questions or statements from all the instruments were examined using 44 items that was thematically grouped into ten guidelines attributes. Although they found that the appraisal tools could help users to judge the quality and utility of clinical practice guidelines, the evidence is insufficient to support the exclusive use of any one of the instruments. The finding suggested that more research is required on the reliability and validity of the appraisal instruments before any one instrument can become widely used.

In addition to the thirteen instruments identified by a previous systematic review, Vlayen et al. (2005) included another eleven appraisal tools in their study. The items of the identified appraisal tools were assessed using ten guideline dimension including the i) validity, ii) reliability/reproducibility, iii) clinical applicability, iv) clinical flexibility, v) multidisciplinary process, vi) clarity, vii) scheduled review, viii) dissemination, ix) implementation, and x) evaluation. The finding indicated that the instruments vary widely in length, scoring system, and comprehensiveness. The number of questions ranged from 2 to 53.

Of 24 appraisal tools, only four addressed all the guideline dimensions including the instruments by the (Scottish Intercollegiate Guidelines Network, 1995), Cluzeau et al. (1999), Helou and Ollenschläger (1998) and The AGREE Collaboration (2003). Of these, the Cluzeau instrument seems to be the most comprehensive and has been validated thoroughly. All dimensions have satisfactory internal reliability (Cronbach's α coefficient: 0.68-0.84) and excellent inter-rater agreement (intra-class correlation coefficient: 0.82-0.90). The instrument consists of 37 items and measures guideline quality in three dimensions: rigour of development, clarity of presentation and applicability (Cluzeau et al., 1999; Lacasse et al., 2001).

The AGREE instrument is another validated and potential instrument that uses a numerical scale, making it easier to compare quality score among guidelines. The instrument is a shorter version of the Cluzeau instrument, containing 23 items divided into six domains: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence (The AGREE Collaboration, 2003). The instrument developed by Shaneyfelt et al. (1999) and Grilli et al. (2000) are others instruments that have been subjected to a validation study. However, further improvement is needed in terms of the quality dimension covered by the instruments.

A more recent systematic review by Siering et al. (2013) identified forty (40) appraisal tools in which eighteen tools had been included in the previous systematic review by Graham et al. (2000) and Vlayen et al. (2005). The study examined the items covered by the appraisal tools and comparisons were made based on thirteen quality dimensions namely: i) information retrieval, ii) evaluation of evidence, iii) consideration of different perspective, iv) formulation of recommendations, v) transferability, vi) presentation of guideline content, vii) alternatives, viii) reliability, ix)

scope, x) independence, xi) clarity and presentation, xii) updating, and dissemination, xiii) implementation, evaluation. The finding indicated that the most comprehensive validated appraisal tool was the AGREE II instrument (The AGREE Next Step Consortium, 2010) of which the instrument met all the thirteen quality dimensions.

However, the AGREE II may not be appropriate in all cases. As the AGREE II instrument only focuses on the methodology aspect and guideline reporting, the ADAPTE (The Adapte Collaboration, 2009) tool is more suitable to assess the quality of clinical content and the GLIA tool (Kashyap N et al., 2011) represents the best choice for assessment of the applicability aspect (Siering et al., 2013).

In conclusion, the choice of appraisal tools mainly depends on the goal of the assessment or the targeted research question because each instrument covers different quality dimensions. The skill of the appraiser and available resources are other important aspects that need to be considered when applying the tools to ensure effective use of the appraisal instrument.

2.4.4 The Appraisal of Guidelines for Research and Evaluation (AGREE)

Instrument

2.4.4.1 The Original AGREE Instrument

In response to the issue of variability in guideline quality, the AGREE Collaboration, a group of international guideline developers and researchers from eleven countries developed and validated an international instrument for assessing the quality of guidelines known as the AGREE instrument. The instrument was published in 2003 and

serves as a generic tool to assess the quality of the methodological aspect and reporting of a guideline (The AGREE Next Steps Consortium, 2009).

The AGREE instrument was developed through a multi-staged process of item generation, selection and scaling, field testing, and refinement process. In the projects, 100 guidelines from the eleven participating countries were assessed by 194 independent appraisers using the instrument. The finding indicated that 95% of the appraisers perceived that the instrument is useful for assessing guideline. The instrument can be used consistently by appraisers of different professions and cultural backgrounds as its reliability was acceptable for most domains (Cronbach's alpha of 0.64–0.88). To that end, the instrument has been accepted as the standard for guideline assessment and endorsed by several health organisations such as the World Health Organization and the Council of Europe (The AGREE Collaboration, 2003).

The instrument comprises of 23 items grouped into six quality dimensions. Each domain assesses a specific dimension of guideline quality, which includes:

- i) Scope and Purpose (items 1-3),
- ii) Stakeholder Involvement (items 4-6),
- iii) Rigor of Development (items 7-14),
- iv) Clarity of Presentation (items 15-18),
- v) Applicability (items 19-21), and
- vi) Editorial Independence (items 22-23).

Each item is rated on a 4-point scale ranging from a score of 4 'Strongly Agree' to 1 'Strongly Disagree', with two midpoint scores: 3 'Agree' and 2 'Disagree'. The scale

measures the extent to which a criterion (item) has been fulfilled (The AGREE Collaboration, 2001).

2.4.4.2 The AGREE II Instrument

a. The Development of the Instrument

In 2009, the original instrument was updated to the AGREE II by the AGREE Next Step Consortium with some improvement in the measurement properties including its reliability and validity to better meet the needs of the users (The AGREE Next Steps Consortium, 2009). The Consortium conducted two series of studies in the project.

The consortium introduced a new seven-point response scale and its performance was evaluated by different stakeholders in the first study (Brouwers et al., 2010b). The 4-point scale in the former AGREE instrument was replaced by a 7-point scale in compliance with the methodology standard of health measurement that is intended to maximize the reliability and discriminability of the instrument (Streiner et al., 2014). In the second study, the consortium assessed the construct validity of the items and user's manual in the new draft of the AGREE II (Brouwers et al., 2010c). Several key findings emerged from the two studies:

- i. Five of six domains were significant predictors of participants' outcome measures ($p < 0.005$).
- ii. All domains and items were rated as useful by the stakeholders (mean score > 4.0) with no significant difference by user type ($p > 0.005$).
- iii. The psychometric properties of the seven-point response scale are acceptable with internal consistency ranged between 0.64-0.89.
- iv. The instrument successfully differentiated between high and low-quality content.

v. The manual was rated as appropriate (all scores above the mid-point of the seven-point scale).

Combination data from the two studies were used by the Consortium to develop the new version of the AGREE II instrument (Brouwers et al., 2010a).

b. Quality Dimension of the AGREE II Instrument

The AGREE II instrument comprised of 23 items grouped into the same six quality dimensions as in the original AGREE instrument and two overall assessment item (The AGREE Next Steps Consortium, 2009). Table 3.2 shows how the 23 items are arranged into the six domains.

Each item is scored using a 7-point Likert scale (1-strongly disagree to 7-strongly agree) based on the extent to which the specific criteria is fulfilled. The overall guideline assessment component of the instrument involves two global rating items, assessing the overall quality of this guideline and recommendation for its use in practice. The overall quality is rated on a 7-point scale (1-lowest possible quality and 7-highest possible quality). The recommendation regarding the use of the guidelines in practice is rated as i) yes, ii) yes with modification, or iii) not recommended based on each clinical area for which the guideline was developed. The consortium recommended that the assessment is carried out by at least two appraisers, and preferably four to increase its reliability. Domain score is calculated by summing up all the scores of the individual items in a domain.

The new user's manual is one of the significant modifications from the original instrument to facilitate efficient and accurate application of the tool (Brouwers et al., 2010b; Brouwers et al., 2010c; Brouwers et al., 2010a). In order to ease understanding

of the users when applying the instrument, information on the AGREE instrument including the on-line training tool is available in the AGREE Research Trust web site <http://www.agreetrust.org> (The AGREE Next Steps Consortium, 2009).

Table 2.3: The complete AGREE II items

Item	Description
Domain 1. Scope and Purpose	
1.	The overall objective(s) of the guideline is (are) specifically described.
2.	The health question(s) covered by the guideline is (are) specifically described.
3.	The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement	
4.	The guideline development group includes individuals from all the relevant professional groups.
5.	The views and preferences of the target population (patients, public, etc.) have been sought.
6.	The target users of the guideline are clearly defined.
Domain 3. Rigour of development	
7.	Systematic methods were used to search for evidence.
8.	The criteria for selecting the evidence are clearly described.
9.	The strengths and limitations of the body of evidence are clearly described.
10.	The methods for formulating the recommendations are clearly described.
11.	The health benefits, side effects, and risks have been considered in formulating the recommendations.
13.	The guideline has been externally reviewed by experts prior to its publication.
14.	A procedure for updating the guideline is provided.
Domain 4. Clarity of presentation	
15.	The recommendations are specific and unambiguous.
16.	The different options for management of the condition or health issue are clearly presented.
17.	Key recommendations are easily identifiable.
Domain 5. Applicability	
18.	The guideline describes facilitators and barriers to its application.
19.	The guideline provides advice and/or tools on how the recommendations can be put into practice.
20.	The potential resource implications of applying the recommendations have been considered.
21.	The guideline presents monitoring and/or auditing criteria.
Domain: Editorial independence	
22.	The views of the funding body have not influenced the content of the guideline
23.	Competing interests of guideline development group members have been recorded and addressed.

c. Using the AGREE II

The AGREE II is a generic tool that can be applied to assess guidelines for use in clinical practice, for formulating policy-related decision or for adaptation from one

context to another. Previous systematic reviews evaluated a wide range of appraisal tools indicated that The AGREE II instrument is one of the most comprehensive validated appraisal tool (Siering et al., 2013). The instrument has been widely accepted as a standard of practice guideline assessment and is endorsed by several international organizations such as the WHO and Guideline International Network (GIN) (Brouwers et al., 2010a; Polus et al., 2012; Brouwers et al., 2012; Siering et al., 2013; Burda et al., 2014; Yu et al., 2014; Kim et al., 2014; Choi et al., 2015).

The instrument not only provides a framework for guideline evaluation but can also be used as a standard for guideline development (The AGREE Next Steps Consortium, 2009; Brouwers et al., 2012; Zeng et al., 2015). The large variation in the way guideline recommendations were developed posed the need to disseminate a standardized method for developing an evidence-based guideline in clinical practice (Simone et al., 2012). The use of the AGREE II instrument as a common standard and checklist for guideline reporting, might also help in improving the validity and reliability of guidelines (Brouwers et al., 2010a).

Many organisations such as National Institute for Health Excellent (NICE) in the UK, The National Federation of Cancer Centers (FNCLCC) in France and The Scottish Intercollegiate Guideline Network (SIGN) have adopted the quality dimensions provided by the AGREE in their guideline programmes, in order to improve the efficiency and effectiveness of guideline development (The AGREE Collaboration, 2003; Scottish Intercollegiate Guidelines Network, 2015).

Zhang et al., (2014) explored the potential influence of the publication of the AGREE II instrument on the quality of guidelines by comparing the quality scores of guidelines published before and after the AGREE II instrument was established. The finding

indicated that guidelines published after publication of the AGREE II instrument significantly scored higher on three domains (scope and purpose, stakeholder involvement, clarity of presentation) as compared with those developed before.

2.4.5 Correlation between Guideline Methodological Quality and Validity of Content

One important limitation in the use of the AGREE instrument is that, the AGREE quality criteria mainly addresses the rigorous development and reporting of a guideline. The instrument does not assess the clinical content and the quality of the supporting evidence, which is a common deficit found in most of the existing appraisal tools. (Vlayen et al., 2005; The AGREE Next Step Consortium, 2010).

One might assume that a guideline with a high-quality score would contain valid recommendations and the assessment of its clinical content is not necessarily needed (Burgers, 2006). This is supported by findings of previous studies indicating evidence-based practice guidelines had statistically significant higher quality scores for AGREE II domains (Zhang et al., 2014; Yanming et al., 2015). An examination of the Anglophone guideline indicated that adherence to the methodological standards resulted in relative homogeneity in several key components of guidelines including their recommendations (Pentheroudakis et al., 2008).

In response to this issue, Watine et al. (2006) conducted a study to test the relationship between the AGREE quality score and recommendation validity in eleven practice guidelines for management of non-small cell lung cancer in laboratory medicine. They found that the AGREE quality score and the recommendations were not

correlated of which practice guidelines with high methodological quality did not necessary contain the most valid recommendations (Watine et al., 2006).

Another study by Nuckols et al. (2008) examined the correlation between guideline acceptability by experts and technical quality of five musculoskeletal disorders. They used the AGREE instrument to assess the technical quality (AGREE standardized domain scores ranged from 0.00 to 1.00). The assessment of clinical acceptability includes two criteria: comprehensiveness (relevance to common clinical situations) and validity (consistency with the experts understanding of existing evidence and opinions). Although they found the guidelines were of excellent technical quality (67% of the domains scores more than 80%), the experts felt that these guidelines omitted common clinical situations and contained recommendations of uncertain validity. Of the topics covered, the expert rated 50% to 69% for comprehensiveness and 6% to 50% for validity (Nuckols et al., 2008).

Both studies indicated that rigorous developed and well-reporting guidelines do not necessary contain appropriate recommendations and are totally accepted by the healthcare providers. The methodological rigour and quality of the clinical content of a guideline are not necessarily correlated. The study suggested that both methodological aspect as well as the clinical content need to be evaluated before implementing a guideline in practice for better patient outcome.

2.5 Focus Group Discussion (FGD).

2.5.1 Introduction

Focus group discussion (FGD) is a qualitative research methodology in which a small group of participants gather to discuss a specified topic or an issue in order to generate data (Kitzinger, 1994; Kitzinger, 1995; Powell & Single, 1996). The unique characteristic of the FGD is the interaction between the moderator and the group members, as well as the added dimension of the interactions among the group members. The group members are able to exchange their ideas, sharing experience on certain issues and comment on each other's opinions during a group discussion. The non-verbal communication and interpersonal communication that can be captured during a group discussion would add a valuable dimension to the data collection which is inaccessible by other forms of qualitative data collections (Kitzinger, 1995; Kidd & Parshall, 2000; Wong, 2008; Krueger & Casey, 2014).

The focus group was first used as a market research technique in the 1920s (Powell & Single, 1996). Apart from being a primary research methods (Liefoghe et al., 1997; Patel & Prince, 2001) the FGD has been used in combination with other qualitative method or quantitative data collection technique (Robotin et al., 2010) to collect supplementary source of data to form a research hypothesis, to generate survey questionnaires or to validate the findings of quantitative research (Dilshad & Latif, 2013).

Focus groups are rapidly gaining popularity in a wide range of health and medical research including the assessment of public experience and understanding of illness (Kitzinger, 1993; Wilkinson, 1998; Patel & Prince, 2001), discovering public's belief

and perception in addition to identifying ideas concerning health-risk behaviour (Duke et al., 1994; Ritchie et al., 1994; Liefoghe et al., 1997). Besides this, investigating health services issues, people responses to policy change or strategy development (Barbour, 1999; Veach et al., 2001; Pastrana et al., 2010), and seeking expert feedback in the development of clinical practice guidelines frequently utilise FGDs too (Roy et al., 2013).

2.5.2 Conducting a Focus Group Discussion

As with other research methods, conducting a focus group require careful planning in order to gain full benefit from the discussion. It involves several processes such as formulating a research question, designing an effective discussion guide, recruiting participants, setting up a focus group session, conducting a Focus Group Discussion, and analysing and reporting the findings (Morgan & Krueger, 1993; Heary & Hennessy, 2002; Merton, 2008; Wong, 2008). The detailed process of the FGD is discussed as follows:

1. Formulating the research question

A specific statement is needed in order to obtain appropriate information from the FGD. It is encouraged to use a narrowly focused topic in FGD, otherwise, the data obtained is likely to be diffused, thus making data analysis a difficult task (Wong, 2008).

2. Designing an effective discussion guide.

The researcher needs to prepare a discussion guide prior to conducting the FGD in order to plan the direction of the discussion and to make data collection more efficient and comprehensive (Wong, 2008). A series of open-ended questions is recommended to be used in order to encourage the participants to respond to the

issues in their own language, generating their own questions and pursuing their own priorities. A moderator may employ other group exercises such as “card game” particularly at the beginning of the session to make them feel comfortable with each other and engage in the discussion (Kitzinger, 1995).

3. Recruiting participants

There are a variety of opinions on the size of an ideal focus group (Masadeh, 2012). It has been suggested that a group of six to ten people is appropriate to obtain adequate participation or it should not be too small that it fails to provide sufficient information of the topic discussed (Powell & Single, 1996; Rabiee, 2004; Dilshad & Latif, 2013).

In terms of group composition, the most appropriate method in recruiting the participants is the “purposive” or “theoretical” sampling (Barbour, 2001), whereby relevant participants are selected based on the characteristics of a target population and the objective of the study (Barbour, 2001; Barbour, 2005).

Most researchers aim for homogeneity within a group or between groups to capitalise on participants’ shared experience. However, in certain occasion, diversity within a group, for example, the present of participants with mixed professions is helpful in exploring different perspectives on certain health issues (Kitzinger & Barbour, 1999). It should be noted that the power hierarchies within particular groups (among individual participants and between participants and the researcher) may suppress honest and spontaneous expression of views by the participants (Williams & Katz, 2001).

4. Setting up a focus group session

The session should be conducted in a comfortable setting to provide a conducive environment for participants to share their ideas, experiences, and attitudes about a topic under investigation. It has been suggested that the participants sit around in a circle to allow eye contact between them (Kitzinger, 1995; Williams & Katz, 2001; Wong, 2008).

5. Conducting a FGD

For each group, it is helpful to work in a team of at least two members including a researcher as the moderator and a research assistant who will do the audio recording and note taking. A moderator is the main player in a FGD who is responsible for guiding the participants through the discussion, as well as looking after the group dynamics to ensure all participants join in the discussion. The focus group can be conducted in a single session of one to two hours duration or more depending on the aim of the research project and available resources. Some researchers conduct the FGD session until it seems that the discussion has reached a saturation point. Ideally, the group discussion should be tape recorded to capture all important information said by the participants (Kitzinger, 1995; Rabiee, 2004; Wong, 2008).

6. Analysing and reporting the findings

Analysis of focus group data involves identification and refinement of themes and subcategories, moving from descriptive to analytical as the researcher attempts to provide an explanation for the pattern identified from the data (Ritchie & Spencer, 2002). The process should be carried out systematically, and verified in order to minimise the potential bias in analysing and interpreting the data (Krueger

& Casey, 2014). However, the data analysed do not generate quantitative information that can be generalised to a larger population (Guba and Lincoln, 1994)

2.5.3 Advantages and Limitation of Using the FGD

The FGD has some advantages and limitations as outlined below:

2.5.3.1 Advantages

1. Generally, focus group research is highly valued as a qualitative research tool due to its ability to generate in-depth insights into a given topic from several people in an efficient and timely manner (Masadeh, 2012). This method is suitable to be used in decision-making process or when a wide range of information needs to be considered in a short period of time because the researcher can identify quickly the full range of perspectives held by the participants during the FGD (Powell & Single, 1996; Heary & Hennessy, 2002).
2. Participants are able to make comments in their own way while being stimulated by thoughts of others in the group. The group dynamic can encourage contribution from people who are either reluctant to be interviewed on their own or unresponsive participants (Kitzinger, 1994).
3. People who cannot read or write or who have other specific disability are not discriminated for giving their opinion (Robinson, 1999).
4. The facilitator can verify data immediately from the participants in the case of ambiguity (Robinson, 1999).

2.5.3.2 Limitations

1. A focus group is susceptible to bias because the group and individual opinions can be swayed by dominant participants or by the moderator. Participants may adopt themes previously raised by the others rather than offer their own opinion. In addition, control over the group discussion could be a problem and time can be lost on issues irrelevant to the original one under investigation (Morgan, 1997; Patel & Prince, 2001).
2. There have also been challenges to the claims made about openness in responding a sensitive or personal issue in a focus group. Kitzinger (1994) in his study on The AIDS Media Research Project found that some respondents were not prepared to share with the group members when sensitive or personal issues were being discussed.
3. Another difficulty associated with the use of focus groups is scheduling a time and location convenient to all participants. Therefore, it was recommended to over-recruit by 10-25% in order to maximise participations (Rabiee, 2004).
4. Qualitative research has its drawbacks, notably limited generalizability due to the recruitment of small, convenience samples. This technique is not useful for testing a hypothesis, statistical testing, and interval estimation, which require quantitative data collection (Morgan, 1997).

Generally, focus group research is highly valued as a qualitative research tool. It is an appropriate method for collecting qualitative data where participants are able to build upon one another's comments, stimulate thinking and discussion, thus generating in-depth insights into a given topic (Powell & Single, 1996; Wong, 2008). Despite some

of the limitations and logistical hurdles involved, this research technique is seen as effective and even less resource needed as compared to other methods (Masadeh, 2012).

2.6 Conclusion.

Firstly, this chapter reviews the principle of management of oral cancer. Generally, the aim of oral cancer management is to eliminate the tumour and any neck nodal metastases, with minimum morbidity to the patient (Brown & Langdon, 1995). The main treatment modalities are surgical removal, radiotherapy or chemotherapy or a combination of these treatment modalities (Fadul et al., 2009; Richardson et al., 2014).

As the management of oral cancer is highly complex, oral cancer is best managed by multidisciplinary teams using an evidence-based framework in order to optimise the quality of care and patient's outcome. By translating the best available scientific evidence into specific recommendations, the guideline can be a useful tool that informs clinician and patients on the best option for cancer care (Burgers et al., 2003a). Consequently, several organisations such the National Comprehensive Cancer Network (NCCN) have been actively involved in the development and updating of CPGs related to oral cancer (National Comprehensive Cancer Network, 2016).

Generally, there are two concepts of guideline development available namely: 1) the "De Novo" development through a systematic appraisal of available evidence and 2) "Guideline Adaptation" which is a systematic approach for customizing the existing guideline(s) by adopting or adapting the recommendations for application in the local context (Graham et al., 2002; Graham et al., 2005). As a number of guidelines on the same topics have been developed by other recognized organizations (Scottish Intercollegiate Guidelines Network, 2006; Belgian Health Care Knowledge Centre,

2014a), the “Guideline Adaptation concept”, using a validated framework provides a possible alternative to the “De Novo” development in order to avoid duplication of effort and to optimise use of resources in developing local CPGs for oral cancer.

However, the quality of the guideline needs to be assessed before adopted or adapted into a new guideline. The AGREE II instrument is one of the most comprehensive validated appraisal tools and has been widely accepted as the standard for assessment of practice guideline for adaption from one context to another (Siering et al., 2013).

Following the Practice Guideline Evaluation and Adaptation Cycle (PGEAC) (Graham et al., 2003), the guideline developers need to select the appropriate methods for obtaining feedback and consensus from a group of experts on the formulated recommendations. Focus group discussion (FGD), a qualitative research methodology is seen as an effective method to be used when the decision-making process needs to be considered within a short period of time. The distinct features of FGD is its group dynamics and the fact that less resource is needed as compared to other methods (Kitzinger, 1994; Kitzinger, 1995; Powell & Single, 1996; Rabiee, 2004).

CHAPTER 3: MATERIALS AND METHODS

3.1 Study Design

The guidelines were developed using a guideline adaptation concept. Mainly, the study employed a combination of:

- 1) Reviewing high quality evidence from the existing 'best practice guidelines' and 'systematic reviews' published since the preparation of the latest selected guidelines (2015-2016).
- 2) Qualitative approach to obtain feedback, refinement and agreement from a multidisciplinary group.

3.2 Study Period

The study was carried out from February 2016 to March 2017.

3.3 Conduct of Study

The framework for evaluating and adapting existing guidelines for local use is adapted from the Practice Guidelines Evaluation and Adaptation Cycle (PGEAC) by Graham et al., (2003). The guideline development process consists of six steps: 3.3.1) identification of clinical areas to promote best practice, 3.3.2) literature search to identify existing guidelines, 3.3.3) assessment of the selected guidelines in terms of quality, currency, and content, 3.3.4) adoption or adaptation of the guidelines for local use 3.3.5) multidisciplinary specialists' feedback and 3.3.6) finalise local guideline. A research committee comprising the researcher and two supervisors of the project were

involved in the decision-making process of every step. The outline of the process is illustrated in Figure 3.1.

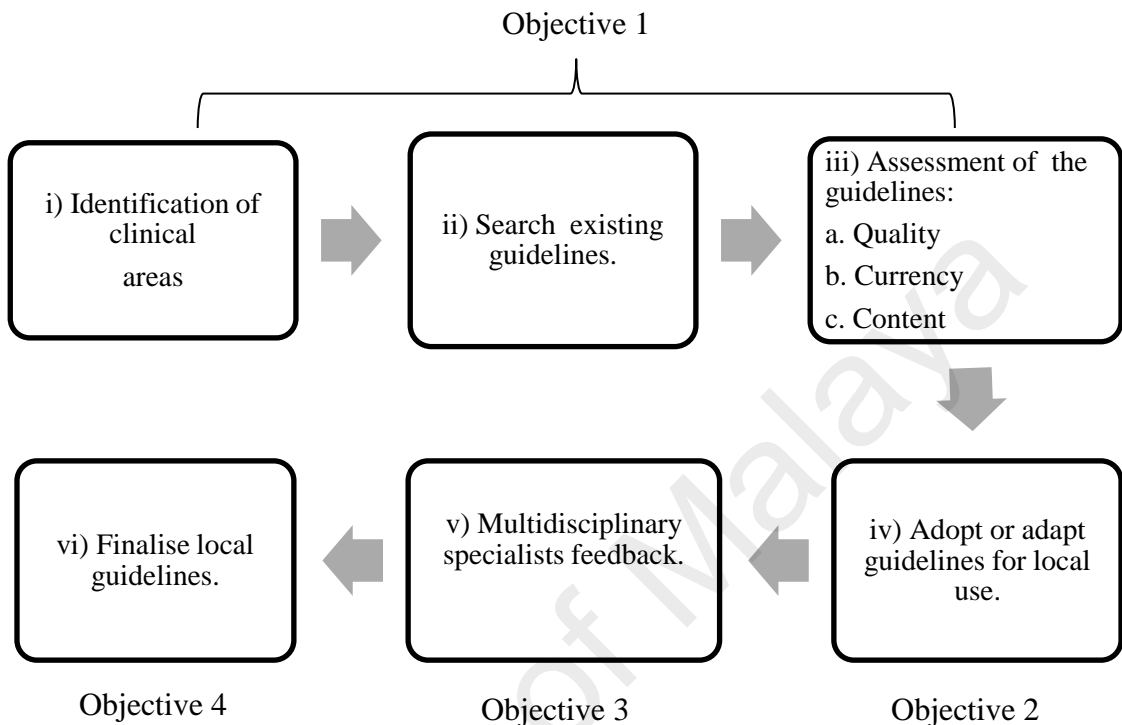


Figure 3.1: Practice guidelines evaluation and adaptation cycle.

3.3.1 Identification of Clinical Areas to Promote Best Practices

Clinical area of interest to promote best practice is the management of oral cancer, which includes diagnosis, treatment, and follow-up care. Selection of the particular clinical areas of diagnosis, treatment and follow up care was based on the existing gaps of care in the management of oral cancer in the country. Besides Clinical Practice Guideline (CPG) on Primary Prevention and Early Detection of Pre-cancerous and Oral Cancer that is already available, guidelines that cover aspects of cancer management from the point of diagnosis throughout treatment until follow up care should be part of the best practices for clinicians to ensure that the quality of care and outcomes for oral cancer patients are optimised.

3.3.2 Literature Search to Identify Existing Guidelines

A systematic literature search for all relevant guidelines related to the clinical area of interest was carried out by computerized search of selected databases and websites as listed in Table 3.1. The selection of the databases and website were based on several guideline adaptation manuals and related literatures (MacLeod et al., 2002; Graham et al., 2002; Graham & Harrison, 2005; The Adapte Collaboration, 2009; Attia, 2013).

In addition, a hand search was also performed on the reference sections of the retrieved articles. The comprehensive search was conducted between 17.02.2016 to 26.3.2016. The search terms used were based on the previous literatures and MeSH terms (Medical subject headings) which included combinations of oral cancer, mouth cancer, head and neck cancer, carcinoma, neoplasm, nodule, mass, tumour, guideline, practice guidelines, clinical practice guideline, best practice, recommendation, consensus statement, consensus, standard (Graham et al., 2002; Graham & Harrison, 2005; Lindsay et al., 2008; Huang et al., 2013). The full search strategies for each database are documented in Appendix A.

Inclusion and exclusion criteria were applied in selecting potential guidelines for this study. The search was limited to guidelines published in English and year of publication from 2000 to 2016. Only guidelines with comprehensive management of oral cancer which includes diagnosis, treatment, and follow-up care were included in this study. Guidelines that focused on a specific stage or type of oral cancer, and focused entirely on a specific procedure, for example, Positron Emission Tomography-Computed Tomography (PET-CT) or Magnetic Resonance Imaging (IMR), were excluded.

A preliminary screening of title and abstract of the articles was carried out by the researcher to identify potential articles that are relevant to the identified clinical area of interest. Articles that met the inclusion criteria were retrieved for full-text review and the duplicates were removed manually beforehand. Based on a full-text review, the basic characteristics of the articles including title, author or organisation of publication, country, the year of publication, update status and clinical area covered by the article are summarized in a table (Appendix B). At this stage, only guidelines which fulfilled the scope of identified clinical area of interest and the most recent version were selected to be included in the development of Malaysian guideline. The decision on which articles to include or exclude was made by the research committee. The decision and reasons for any exclusion are recorded in Appendix B.

Additional documents related to the development process of the selected guidelines were retrieved from the guideline developers' websites. Eight guidelines' developers including The Saskatchewan Cancer Agency, Johan Fagan, South Australia Cancer Service, British Association of Otorhinolaryngology, European Society for Medical Oncology, National Institute for Clinical Excellence, Cancer Care Nova Scotia, and Spanish Society for Medical Oncology were contacted through email to obtain such supplemental documents that were not available from their websites. The first four authors of the guidelines responded to the email and provided the documents and information about their guideline development. The subsequent three guidelines' developers uploaded the related document to their websites and the last guidelines' author did not respond at all to the email.

Table 3.1: List of databases and websites for search of existing guidelines

NO	WEBSITE	URL
Clinical practice guidelines databases		
1.	National Guideline Clearinghouse (NGC)	http://www.guidelines.gov/
2.	Guideline International Network (G-I-N)	http://www.g-i-n.net/
3.	Canadian Medical Association Infobase (CMA)	http://mdm.ca/cpgsnew/cpgs/index.asp
4.	SAGE directory of Cancer Guideline (SAGE)	http://www.cancerview.ca/cv/portal/Home/TreatmentAndSupport/TSPProfessionals/ClinicalGuidelines/GRMain/GRCSAGE/
Guideline developer websites		
5.	Ontario Guideline Advisory Committee (GAC) Recommended Clinical Practice Guideline	http://www.gacguidelines.ca
6.	Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/knowledge/
7.	New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
8.	Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk.guidelines/index.html
Medical Oncology Society		
9.	American Society of Clinical Oncology (ASCO)	http://www.asco.org
10.	National Cancer Institute (NCI)	http://www.cancer.gov
11.	American Society for Therapeutic Radiation and Oncology (ASTRO)	https://www.astro.org/
12.	British Association of Head and Neck Oncologist (Bahno)	bahno.org.uk/
13.	European Society for Medical Oncology (ESMO)	http://www.esmo.org/
14.	Cancer Care Ontario (CCO)	http://www.cancercare.on.ca
15.	National Comprehensive Cancer Network (NCCN)	http://www.nccn.org
16.	European Society for Radiotherapy and Oncology (ESTRO)	www.estro.org/
Medical Specialties Society/ Government Agencies		
17.	Food and Drug Administration (FDA)	http://www.fda.gov/cder/guidance/index.htm
18.	SOR: Standard, option et recommendations (SOR).	http://www.fnclcc.fr/-sci/sor/index.htm
19.	Registered Nurses Association of Ontario (RNAO)	http://www.mao.org
20.	Agency for Quality of Medicine (AQM)	http://www.aeqz.de
21.	National Institute of Health (NIH)	http://www.nih.gov/
22.	Agency for Health Care Research and Quality (AHRQ)	http://www.ahrq.gov/
23.	National Health and Medical Research Council (NHMRC)_Australia	https://www.nhmrc.gov.au/guidelines-publications
24.	National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/guidance
Published literature databases		
25.	TRIP Database	http://www.tripdatabase.com
26.	Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database	http://www.york.ac.uk/inst/crd/
27.	Cochrane Library	www.cochranelibrary.com/
28.	MEDLINE	http://www.ncbi.nlm.nih.gov/pubmed
29.	EMBASE	http://ezproxy.um.edu.my:2232/#quickSearch/default
Others		
30.	Google	http://www.google.com/
31.	Yahoo	https://www.yahoo.com/

(MacLeod et al., 2002; Graham et al., 2002; Graham & Harrison, 2005; The Adapte Collaboration, 2009; Attia, 2013).

3.3.3 Assessment of Guidelines

A critical assessment was carried out on the selected guidelines, to identify the most appropriate guidelines for adoption or adaptation as the Malaysian guideline. It involved three separate assessments namely: i) quality of the guidelines ii) guideline currency and iii) clinical content of the guideline's recommendations. The details of the assessment are described in the following sections.

3.3.3.1 Assessment of Guidelines: Quality

a) Appraisal Instrument

A systematic assessment of the methodological quality and reporting of the selected guidelines was carried out using The Appraisal of Guidelines Research and Evaluation II instrument (AGREE II) (The AGREE Next Step Consortium, 2010). The AGREE II is used because it has become a widely accepted standard as guideline appraisal instruments and has been endorsed by the World Health Organization, the Council of Europe and the Guidelines International Network (The AGREE Collaboration, 2003).

The instrument consists of 23 items organized into six domains and two overall assessment items. Each domain assesses a specific dimension of guideline quality, which includes: i) Scope and Purpose, ii) Stakeholder Involvement, iii) Rigor of Development, iv) Clarity of Presentation, v) Applicability, and vi) Editorial Independence. The details description of the items and the rating scale are discussed in the Chapter 2, section 2.4.4.2 The AGREE II instrument.

b) Evaluation of the Guidelines

Two public health specialists from the Oral Health Division, Ministry of Health who are experts in guideline development were selected to participate as the appraisers for this study. Permission to involve the two methodology experts in this study was obtained from their head of department (Director of Oral Health Division, Ministry Of Health Malaysia) (Appendix C). Prior to evaluating the guidelines, both appraisers were briefed about the purpose of the work and received the following documents: i) a list of guidelines included in the assessment and the supplement materials related to the guidelines, ii) a copy of each guideline with their supplement materials, iii) the AGREE II User's Manual: updated September 2013, iv) fifteen (15) sets of AGREE II Instrument (The AGREE II instrument and its manual can found at (<http://www.agreetrust.org>) and v) terms of references for quality assessment of guidelines.

The quality assessment was conducted over a five-month period from April 2016 to August 2016, in two stages: i) screening of all selected guidelines using the Domain Rigour of Development of the AGREE II instrument, followed by ii) complete Agree II appraisal by using all six domains. Both appraisers assessed each of the guidelines independently and they did not communicate with each other during the appraisal process. When both appraisals were completed, they were permitted to share and discuss their results to clarify discrepancies, particularly if the scoring differed more than 3 points on any ítem between them.

Stage I: Screening of Guideline Using the AGREE's 'Rigour of Development' Domain

The guideline search found a substantial number of potentially relevant guidelines. The research committee decided to reduce the number of guidelines for complete AGREE II appraisal, given the potential time and work burden of the appraisal process. At this initial stage, both appraisers screened all selected guidelines using the Domain Rigour of Development of the AGREE II instrument to identify the higher quality and rigorously developed guidelines for further assessment using all AGREE II domains. (The Adapte Collaboration, 2009). The Rigour of Development domain is considered more important than other domains as the eight (8) items comprising this domain measure the degree to which the guideline development process was evidence-based (Graham & Harrison, 2005).

Upon completion of the screening, the completed AGREE II instruments with Domain Rigour of Development scores were collected from the appraisers. The results of the rigour scores were scrutinized a cut-off point for the acceptable quality score for that Domain was set as 60% by the research committee. The decision was based on the comparison of rigour scores across the evaluated guidelines and the level of acceptable quality score reported in the previous studies (Burgers et al., 2004; Alonso-Coello et al., 2010; Zhang et al., 2014; Yanming et al., 2015). Subsequently, only evidence-based guidelines which scored above the cut-off point for Domain Rigour of Development were retained at this point.

Stage ii) Complete AGREE II Appraisal

At the second stage of assessment, the appraisers evaluated the remaining guidelines using the other five AGREE II domains and two overall guideline assessment items on

the same AGREE II instrument as before. Upon completion, the completed appraisal scores were reviewed by the research committee. The research committee then selected the potential guidelines for adoption or adaptation as local guidelines based on the following quality criteria:

1. Overall quality ratings of all domains. The acceptable quality score cut-off point for all domains was retained at 60%.
2. Recommendation regarding the use of the guidelines in practice by the appraisers.
3. Context and format of the guidelines.

c) Data Handling and Analysis

For the purpose of data analysis, the raw appraisal scores for each domain were tabulated in Microsoft Excel 12.0 Spreadsheet. As there were no discrepancies or errors in rating score as adjudged by the appraisers and researcher, no adjustments on the data sheet were needed. A quality score was calculated independently for each of the six AGREE II domains using the formulas as described in the AGREE II User's Manual. Domain scores were calculated by summing up all the scores of the individual items in a domain and the total was standardized as a percentage of the maximum possible score for that domain (ranged from 0% to 100%) (The AGREE Next Step Consortium, 2010). Standardized domain scores were calculated as follows:

Obtained score: The sum of all scores of the individual items given by all appraisers in a domain.

Maximum possible score: 7 (strongly agree) x y (items in a domain) x 2 (appraisers)

Minimum possible score: 1 (strongly disagree) x y (item in a domain) x 2 (appraisers)

Standardized domain score:
$$\frac{\text{Obtained score} - \text{Minimum possible score}}{\text{Maximum possible score} - \text{Minimum possible score}}$$

Statistical analysis was performed using the Statistical Package for the Social Sciences Software (v. 22.0; SPSS; Chicago). The mean, standard deviation and median were calculated to describe the average quality score for each domain. The inter-rater reliability within each domain was determined by the intra-class correlation coefficient (ICC). The ICC must be at least 0.7 for the agreement between appraisers to be adequate (Terwee et al., 2007).

3.3.3.2 Assessment of Guidelines: Currency

Based on the earlier assessment, guidelines that met the quality criteria were further assessed on whether they are still current and relevant for the adaptation process. This is to ensure that the most current evidence is included in developing recommendations for the local guideline. Studies have recommended that a guideline should be reviewed regularly within as little as three years, depending on the research activity of the clinical area in order to keep the practice guidelines up-to-date (Shekelle et al., 2001b; Shekelle et al., 2001a). In this study, several methods were used for checking the guideline currency including:

1. Reviewing the date of release or publication of the guidelines.
2. Reviewing the bibliography list for the dates or period covered by the literature to determine whether the most current evidence has been included.
3. Checking with the guideline developers for the guideline status whether the related guidelines are still in use and also their update plans. A guideline currency survey (Appendix D) was adapted from the Guideline Adaptation: A resource kit (Adapte Collaboration, 2009). The questionnaire comprised of four

questions to ascertain whether the guideline developers is aware of new evidence relevant to their guidelines or new evidence that could invalidate any of the recommendations comprising the guidelines, the guidelines update status and finally on the plans to update the guidelines. The surveys were emailed to all developers of the shortlisted guidelines based on the complete AGREE II appraisal (see 4.2.1.2 (C)).

3.3.3.3 Assessment of Guidelines: Clinical Content

Content analysis is the final step in the guideline assessment. This process was carried out to systematically assess the clinical content of the recommendations in each of the shortlisted guidelines (based on the quality and currency assessments). The assessment consisted of three parts including a) preparation of the recommendation matrix, b) identification of systematic reviews on oral cancer management and finally c) assessment of the guideline recommendations. The detailed of each part is discussed below:

a) Preparation of the Recommendation Matrix for Oral Cáncer Management

All recommendations with the corresponding levels of supporting evidence were extracted from the shortlisted guidelines and were tabulated in a table known as recommendation matrix (Appendix E). The matrices were used by the panel to compare various aspects of the recommendations between the guidelines. These guidelines recommendations were grouped according to the clinical area of interest namely: diagnosis, treatment and follow-up care. All guidelines used different grading systems to classify their level of supporting evidence (Table 3.2). The levels of the supporting evidence used by the guideline developers were reclassified into a new scale namely:

high level evidence (High), low level evidence (Low) and good practice point (GPP) for purposes of comparing recommendations between the shortlisted guidelines within the matrix. The new classification for the level of the supporting evidence is documented in Table 3.3.

Table 3.2: Grading system of the evidence used by each of the guideline developer

GUIDELINE DEVELOPERS	LEVEL OF EVIDENCE	DESCRIPTION
National Comprehensive Cancer Network (NCCN).	NCCN CATEGORIES	
	High level evidence	Large, well designed, randomised controlled trials (RCTs).
	Low level evidence.	Indirect comparisons among randomised trials, phase II or non-randomised trials, smaller trials, retrospective studies, or clinical observations.
Belgian Health Care Knowledge Centre.	GRADE SYSTEM	
	High	RCTs without important limitations or overwhelming evidence from observational studies
	Moderate	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies.
	Low Very Low	RCTs with very important limitations or observational studies or case series.
Scottish Intercollegiate Guideline Network (SIGN).	SIGN CLASSIFICATION.	
	1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
	1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
	1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
	2++	High quality systematic reviews of case control or cohort studies, or high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
	2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
	2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
	3	Non-analytic studies, e.g. case reports, case series.
	4	Expert opinion.
Good Practice Point (GPP)	Recommended best practice based on the clinical experience of the guideline development group.	

Table 3.3: The new classification for the level of the supporting evidence

LEVEL OF EVIDENCE	DESCRIPTION
High level evidence (High)	Evidence from meta-analysis, systematic review of randomised control trials (RCT), high quality systematic reviews of case control or cohort studies, RCT and high quality case control or cohort studies with a very low risk of confounding or bias.
Low level evidence (Low)	Evidence from non-randomized trials, well conducted case controls, cohort studies, case reports, case series, expert opinion, clinical observation.
GPP	Recommended best practice based on the clinical experience of the guideline development group.

b. Identification of Systematic Reviews on Oral Cancer Management

An additional search was conducted to identify systematic reviews that were published more recently, that is, since the preparation of the latest selected guidelines. This search and documentation was intended to fill the gaps of the current evidence pertaining to the management of oral cancer which was not covered by the selected guidelines. The most recent guidelines covered literature from 1955 to 2014. Therefore, the additional search covered literature published from 2015 to October 2016.

The search strategy was based on the definition of PICO (Table 3.4). However in the search strategy, only the component P and I (including all synonyms) were used, in order to prevent the search from being too restrictive. The search strategy focused on the databases as listed in Table 3.5. In addition, a hand search was conducted on the reference list of the relevant systematic reviews. The full search strategy is available in Appendix F.

Table 3.4: The description of PICO terms

TERMS	DESCRIPTION
Population	Oral cancer or head and neck cancer.
Intervention	Diagnosis, treatment, follow-up care, surgery, radiotherapy, chemotherapy.
Control/Context	Not applicable
Outcomes	Quality of care, survival, locoregional control, disease-free survival progression-free survival and quality of life.

Table 3.5 Databases used to identify the systematic reviews

NO.	WEBSITE	URL
1.	TRIP Database	http://www.tripdatabase.com
2.	Database of Abstracts of Reviews of Effectiveness (DARE)	www.york.ac.uk/inst/crd
3.	The Cochrane database of systematic reviews	http://www.cochrane.org
4.	MEDLINE	http://www.ncbi.nlm.nih.gov/pubmed

Articles published only in English were included in the study. A preliminary screening of title and abstract of the articles was carried out by the researcher to identify relevant systematic reviews pertaining to the management of oral cancer. Articles that met the inclusion criteria were retrieved for full-text review and the duplicates were removed manually beforehand. Based on the full text-review, the basic characteristics of the articles including title, author, the year of publication, journal citation were recorded (Appendix G). Finally, systematic reviews that fulfilled the inclusion criteria were selected to be included for an update of the current evidence pertaining to the management of oral cancer. The excluded articles were highlighted in grey and the reasons for exclusion were recorded in Appendix G. The detailed information of the selected systematic reviews was summarized in evidence tables (Appendix H).

c. Assessment of the Guideline Recommendations

An expert panel comprising interdisciplinary specialists namely an Oral Maxillofacial Surgeon, an Oral Pathologist, an Orthorhinolaryngologist, and a Clinical Oncologist were involved in this process. The former two panel members are from Faculty of Dentistry, University of Malaya and the latter two are from University of Malaya Medical Centre. The role of the panel was to assess the recommendations of the shortlisted guidelines and select the most appropriate ones to be included in the Malaysian guidelines. The assessment process was undertaken over a month period (November 2016). Prior to evaluating the guideline recommendations, all expert panel members were briefed about the work processes and were provided with the following documents:

1. Terms of Reference for Content Analysis of Guidelines.
2. Recommendation Matrix of Oral Cancer Management of the Shortlisted Guidelines.
3. Assessment forms for each shortlisted guideline.

Firstly, the panel reviewed each recommendation in the recommendation matrix independently and recorded recommendations to include or exclude into the local guideline. The selection of the recommendations was based on the three factors as follows:

1. Their impact on quality of care for patients.
2. Level of evidence supporting the recommendations.
3. Applicability and feasibility of implementation in the local context.

The panel was given the options, either accepting each recommendation, modifying them or adding to them based on evidence or their clinical experience. In performing

this assessment, each expert panel member filled separate assessment forms for each guideline. Subsequently, the completed assessment forms were collected from each panel member (by the researcher) and their individual rating and comments were combined and recorded onto new assessment forms (Appendix I, Appendix J, Appendix K).

3.3.4. Adopt or Adapt Guidelines for Local Use

3.3.4.1 Consensus on the Final List of Recommendations for the Malaysian Guidelines

After the expert panel had completed their individual assessments, a follow-up meeting was arranged by the researcher to discuss the findings and to seek the expert panel's (4 members) consensus on the final list of recommendations to be included in the local guideline. The meeting was attended by the researcher, supervisor of the research project and the expert panel members. During this meeting, the researcher presented the findings of the expert panel's independent assessment.

An informal group discussion was used to achieve consensus on the final list of recommendations among the expert panels. The decisions made by the expert panel were recorded in Appendix I, Appendix J and Appendix K.

3.3.4.2 The Draft Guideline

The draft was prepared by the researcher based on the final list of recommendations that was agreed upon by the expert panel. The draft was then reviewed by the research committee (supervisors of the research project). The format and content of the draft were adapted from the Guideline Adaptation: A Resource Toolkit by the ADAPTE

Collaboration (The Adapte Collaboration, 2009) and two guidelines that were developed using the concept of “Guideline Adaption” (Gilbert et al., 2009; Alberta Health Services, 2014). The sections included in the draft guideline and the descriptions are illustrated in Table 3.6.

Table 3.6: The content sections included in the draft guideline

SECTION		DESCRIPTION
LIST OF ABBREVIATIONS		
ALGORITHM FOR MANAGEMENT OF ORAL CANCER		
1.0 SECTION 1: INTRODUCTION.		
1.1	Background	A brief description of the burden of the condition, the importance of health care intervention and the rationale for the guideline development.
1.2	Objective	Describes the objective for developing the guideline.
1.3	Target population	Describes the population of interest.
1.4	Target users	Describes the intended user of the guidelines.
2.0 DEVELOPMENT OF THE GUIDELINES		
2.1	Development of the guidelines	Describes the process involved in the guideline development.
2.2	Review and update	Describes when the guidelines will be reviewed and updated.
2.3	Acknowledgement	Express gratitude and thanks to whom involved in the development of the guideline.
2.4	Declaration of conflict of interest	Provides information on potential conflict of interest.
2.5	Funding	Provides information on the funding source.
2.6	proposed clinical audit indicators for quality management	Describe indicator to be used in monitoring and evaluating the effectiveness of the guide.
3.0 CLINICAL RECOMMENDATIONS		
3.1	Clinical recommendations.	Provides full clinical recommendations for the management of oral cancer in Malaysia including diagnosis, treatment and follow-up care. Each recommendation is listed with the sources and provided with the level of the supporting evidence.
3.2	Summary of evidence	Provides detailed summary of the evidence used to develop the guideline recommendations.
REFERENCES		
APPENDICES		

3.3.5 Multidisciplinary Specialists Feedback

Qualitative approach using the Focus Group Discussion (FGD) technique was chosen to obtain feedback from the multidisciplinary specialists regarding the draft guideline. The advantage of using a focus group technique is that participants are able to build upon one another's comments, stimulate thinking and discussion, and consensus can be achieved quickly. Moreover, the group process allowed the participants to contribute in the development of the guideline and develop ownership of the resulting decisions (Powell & Single, 1996; Wong, 2008) in order to encourage the uptake of the guideline in the local practice.

3.3.5.1 Purpose of the Focus Group Discussion

- 1) To obtain general feedback regarding the format of the draft guideline, Section 1(Introduction), and Section 2 (Development of the Guideline).
- 2) To refine and reach consensus on Section 3: Clinical Recommendations.

3.3.5.2 Sample Population

The FGD involved multidisciplinary specialists comprising Oral Maxillofacial Surgeons, Oral Medicine and Oral Pathologists, and Dental Public Health Specialists. Oral Maxillofacial Surgeons, Oral Medicine and Oral Pathologists with at least five years clinical experience in managing oral cancer patients throughout Malaysia were selected. The Dental Public Health Specialists were chosen based on their prior involvement with guidelines development and role in coordinating oral cancer programmes in the state/country.

3.3.5.3 Sampling Technique

Purposive sampling method was used in selecting representatives of multidisciplinary specialists from public and private universities and Ministry of Health, Malaysia for the focus groups.

3.3.5.4 Sample Size

Twelve multidisciplinary specialists comprising eight Oral Maxillofacial Consultants, two Oral Medicine and Oral Pathologist Consultants, and two Senior Dental Public Health Specialists (considered as clinical and methodological experts) were identified as potential participants for the FGD.

3.3.5.5 Recruiting the Focus Group

The researcher personally contacted the potential participants through telephone to confirm their interest and availability to take part in the FGD. The potential participants were briefed on the objectives of the FGD and the process involved. Their role in the FGD was also made clear to them.

As a follow-up to the telephone call, an invitation letter was sent to each of them. These invitation letters provided the information about the FGD meeting including the date, time, venue and the tentative agenda. The participants were provided with the draft guideline three weeks prior to the FGD meeting to give them adequate time to read it. The participants were reminded again through a telephone call two days before the scheduled FGD to ensure their presence at the meeting.

3.3.5.6 Conduct of the Focus Group Discussion

Data were collected through one Focus Group Discussion. The group meeting was conducted on 13.03.2017 at the Dental Specialist and Research Tower, Faculty of Dentistry, University of Malaya. The FGD was facilitated by the researcher. A research assistant took notes on the discussion content and assisted in recording the discussions using an audiotape. The discussion was recorded to capture all relevant points for data collection.

The structure of the meeting was based on the method suggested by Kitzinger (1995) and Wong (2008). The process of the Focus Group Discussion is documented in the Figure 3.2. The FGD was guided by structured predetermined open ended questions in order to stimulate discussion among the participants, to make data collection more efficient and to ensure the topic were well covered during the group discussion. Mainly the discussion focused on the format of the guideline and the three main sections of the guideline including: Section 1 (Introduction), Section 2 (Development of the Guideline) and Section 3 (Clinical Recommendations). The set of questions for each section is presented in Appendix L.

During registration, each participant was given a Participants Information Sheet outlining the purpose and procedure to be followed, a Consent Form and a Declaration of Competing Interest Form.



The FGD began with welcome remarks to the participants followed an introduction of the facilitator about herself, the research assistant and the supervisors of the research project.



Introduction: The facilitator gave a brief overview of the FGD.

1. Objectives of the FGD.
2. Role of the panel members.
3. Procedure and rules.
4. Objective of the study and study methodology.
5. Duration of the discussion.



Ice breaking session: Participants were asked to introduce themselves. The participants were also reminded to sign the Consent Forms and Declaration of Competing Interest Form prior to the FGD.



The FGD commenced with the facilitator asking the participants general questions on:

- i. Format of the guideline.
- ii. Section 1(Introduction)
- iii. Section 2 (Development of the guideline).



The FGD continued with Section 3 (Clinical Recommendation). Participants were asked to read and deliberate on each clinical recommendation in order to refine and reach a consensus.



The facilitator summed up the main points of the discussion before the session end. The participants were thanks for their willingness to participate in the focus group.

Note: During the entire FGD process, the facilitator ensured that consensus was reached for each section before moving to the next section.

Figure 3.2: The process of the focus group discussion

3.3.5.7 Data Analysis

a) Data Transcription

The audio recorded data of the FGD was transcribed by the researcher to produce a verbatim transcript of the entire discussion. The complete transcript was then compared with the handwritten notes taken by the research assistant. Additional comments (from the handwritten notes) were inserted into the transcript where appropriate to fill in any existing gaps of the verbatim transcript.

b) Analysing the Data

The researcher read the complete transcript. The data in the transcript were then coded to extract comments and feedback by the specialists regarding the i) format and ii) contents of section 1, 2 and 3 in the draft guideline for Malaysia. Also, other emerging themes from the FGD were noted. The complete transcript was analysed and interpreted accordingly using NVIVO version 11.0.

3.3.5.8 Ethical Consideration

The research project was approved by the Medical Ethics Committee, Faculty of Dentistry, University of Malaya (reference no: DF CO1602/0004(P)) on 19.02.2016 (Appendix M) and Medical Research Ethics Committee MREC, Reference no:(5)KKM/NIHSEC/P16-472 on 1.04.2016 (Appendix N). The agreement for involvement of multidisciplinary specialists at government hospitals was obtained from the Principal Director of Oral Health, Ministry of Health Malaysia on 3.08.2016 (Appendix O).

Consent and permission for the audio recording were obtained from the participants prior to the FGD. Confidentiality was ensured by omitting personal details from the discussion content and the responses were kept anonymous. Participants were asked to complete a Declaration Form of Competing Interest detailing the sources of funding, and other possible conflicts of interest. At the completion of the study, the records will be kept confidential at the Department of Community Oral Health and Clinical Prevention, University of Malaya for two years and will be destroyed after the period if no further action is required.

3.3.6 Finalising Best Practice Guidelines for Oral Cancer Management in Malaysia

All feedback received from the multidisciplinary specialists were taken into consideration and modifications of the guideline were made (by the researcher) based on their comments and suggestions. The modified draft guideline was reviewed by the project supervisors. After the guideline contents had been refined, the second version of the draft guideline was emailed to all FGD participants to seek their feedback and to reach consensus among them. The final version of the best practice guideline was then formatted based on the consensus achieved by these multidisciplinary specialists.

CHAPTER 4: RESULTS

In this chapter, results are presented as follows:

4.1 The finding of the literature search in identifying existing guidelines for adaptation.

4.2 The assessment of guidelines in terms of:

4.2.1) Quality

4.2.1.1) Domain Rigour of Development scores of the 15 guidelines.

4.2.1.2) Complete AGREE II's domains appraisal across the shortlisted guidelines.

4.2.2) Currency

4.2.3) Clinical Content

4.3 Results on whether to adopt or adapt guidelines for local use.

4.4 The multidisciplinary specialists' feedbacks regarding the draft guidelines for oral cancer management in Malaysia.

4.5 The final best practice guideline is presented in the last section of the chapter.

4.1 Literature Search to Identify Existing Guidelines

The literature search of selected databases and websites yielded 3,192 potentially relevant articles and no new guidelines were identified through reference list searches. Of these, 3,068 articles were initially excluded based on titles and abstracts for the following reasons: i) articles could not be considered as guidelines or oral cancer guidelines (n= 2,745), ii) guidelines were focussed entirely on a specific procedure, for example, IMRT, PET-CT and Epidermal growth factor receptor (EGFR) targeted therapy (n=235), iii) the scope of the guidelines were beyond the clinical area of interest, for example screening and prevention (n=73), iv) guideline development in progress (n=3), and v) articles were not in English (n=12).

From the remaining 124 articles, 91 duplicate articles were removed manually. This resulted in a total of 33 articles included for full-text review (Appendix B). After reviewing the full-text, another 18 articles were excluded because they could not be considered as guidelines (review articles that highlight the recent updates of a clinical practice guidelines) (n=3), guideline that focussed entirely on the radiotherapy procedure (n=1), the scope of the guidelines were beyond the clinical area of interest, of which the guidelines focussed on the prevention procedures (n=3) and the guidelines had been replaced by a more recent version (n=11). The detailed description of the guidelines and reasons for any exclusion are stated in Appendix B (excluded articles are highlighted in grey in the table). Finally, fifteen potential guidelines that fulfilled the inclusion and exclusion criteria were considered for adaptation or adoption in the development of Malaysian guideline (Table 4.1). Figure 4.1 illustrates the results of the guideline selection process.

4.1.1 Characteristic of the 15 Potential Guidelines

Table 4.1 illustrates the characteristics of the shortlisted 15 selected guidelines. Of the 15 guidelines, 11(73 %) had been published from 2010 onward. Seven (47%) of the guidelines were developed in Europe, followed by four (26%) from Canada, two (13%) from Australia and one each (7%) from the United States of America and South Africa. Eight (53%) of the guidelines were developed by medical societies while the others six (40%) were developed by government agencies, and one (7%) by an academic organisation. Among the guidelines, twelve (80%) were the first editions and only three (20%) had been updated at least once.

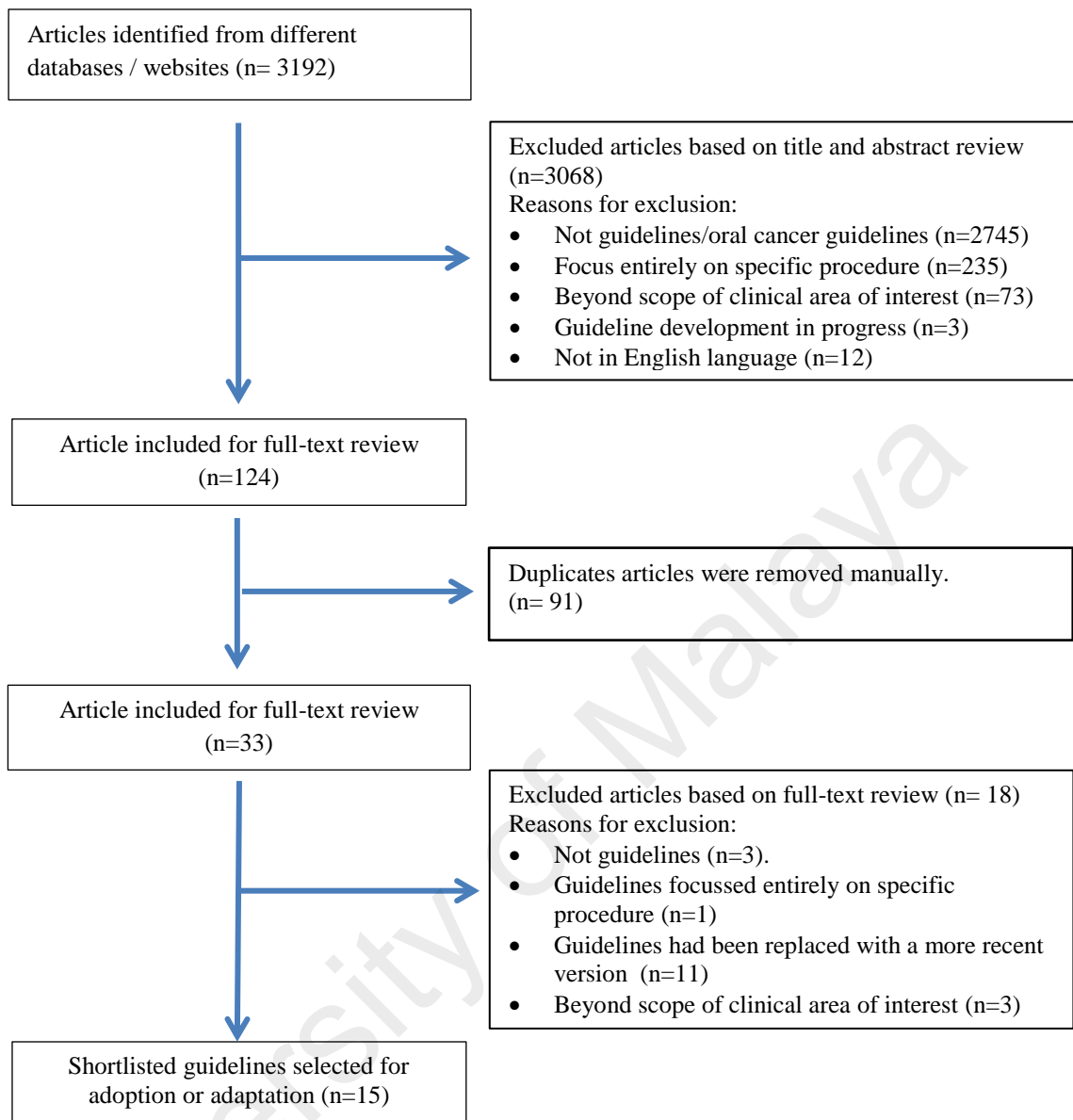


Figure 4.1: Results of the guidelines selection process

Table 4.1: Characteristics of the selected guidelines that were finally shortlisted

No	Developer	Guidelines Title	Country/ Region	Year of publication	Status
1.	National Comprehensive Cancer Network	NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Head and Neck Cancer. Version 1.2015.	The United States of America	2015	Update
2.	The Saskatchewan Cancer Agency	Provincial Oral Cavity Cancer Treatment Guidelines.	Canada	2015	New
3.	Victoria Government	Optimal Care Pathway for People With Head and Neck Cancers.	Australia	2015	New
4.	Belgian Health Care Knowledge Centre	Oral Cavity Cancer: Diagnosis, Treatment, and Follow-up.	Belgium	2014	New
5.	Alberta Health Services.	Clinical Practice Guidelines HN-002. Oral Cavity Cancer.	Canada	2014	New
6.	Fagan et al., Division of Otolaryngology University of Cape Town	Management Principles / Guidelines for Head and Neck Cancer in Developing Countries.	South Africa	2014	New
7.	South Australian Cancer Service	South Australian Head and Neck Cancer Pathway.	Australia	2013	New
8.	Spanish Society for Medical Oncology (SEOM)	SEOM Clinical Guidelines for the Treatment of Head and Neck Cancer (HNC).	Spain	2013	New
9.	German Cancer Society	Clinical Practice Guideline: The Diagnosis and Treatment of Oral Cavity Cancer.	German	2012	New
10.	British Association of Otorhinolaryngology	Head and Neck Cancer: Multidisciplinary Management Guidelines 4 th edition.	United Kingdom	2011	Update
11.	European Society Medical Oncology	Squamous Cell Carcinoma of the Head and Neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-up.	Europe	2010	Update
12.	Cancer Care Ontario	The Management of Head and Neck Cancer in Ontario.	Canada	2009	New
13.	Cancer Care Nova Scotia	Guidelines for the Management of Head and Neck Cancers (excluding Thyroid).	Canada	2007	New
14.	Scottish Intercollegiate Guideline Network	Diagnosis and Management of Head and Neck Cancer. A National Clinical Guideline.	Scotland	2006	New
15.	National Institute for Clinical Excellence	Guidance on Cancer Services – Improving Outcomes in Head and Neck Cancers – The Manual.	United Kingdom	2004	New

4.2 Assessment of Guidelines.

4.2.1 Assessment of Guideline: Quality

4.2.1.1 Domain Rigour of Development Scores of the 15 Guidelines

At the completion of the assessment, the completed AGREE II instruments for all 15 guidelines were collected from both appraisers. The results of the Domain Rigour of Development scores according to the guideline developers are presented in Table 4.2. The quality scores for Domain Rigour of Development was highly variable (range: 11% to 92%) with a clear distinction between the high and low quality guidelines. The mean score was 58.7 ± 28.5 . The ICC value for this domain was 0.9. This result indicated that the overall agreement between both appraisers in this domain was good.

Comparison of the Domain Rigour of Development scores across the 15 guidelines showed that the Scottish Intercollegiate Guideline Network guideline scored the highest (92%) and the Saskatchewan Cancer Agency guideline scored the lowest (11%). Based on the predetermined acceptable quality score for this domain (set by the research committee), slightly more than half, or 8 (53%) of the guidelines scored higher than 60%. These were guidelines produced by the Scottish Intercollegiate Guideline Network, Cancer Care Ontario, Belgian Health Care Knowledge Centre, National Institute for Clinical Excellence, National Comprehensive Cancer Network, Alberta Health Services, German Cancer Society and Victoria Government. Based on the results, the research committee decided to keep the eight guidelines for further assessment using complete AGREE II domains. The guidelines that scored poorly (< 60%) in this domain were excluded by the research committee (Table 4.2).

Table 4.2: AGREE II domain rigour of development scores across the 15 guidelines

No.	Guideline's developer	Domain Rigour of Development
1.	Scottish Intercollegiate Guideline Network, 2006 (SIGN).	92%
2.	Cancer Care Ontario, 2009 (CCO).	91%
3.	Belgian Health Care Knowledge Centre, 2014 (BKCE).	88%
4.	National Institute for Clinical Excellence, 2004 (NICE).	84%
5.	National Comprehensive Cancer Network, 2015 (NCCN).	82%
6.	Alberta Health Services, 2014 (AHS).	77%
7.	German Cancer Society, 2012 (GCS).	76%
8.	Victoria Government, 2015 (VG).	75%
9.	British Association of Otorhinolaryngology, 2011 (BAHNO)	44%
10.	South Australia Cancer Service, 2013 (SACS).	40%
11.	Cancer Care Nova Scotia, 2007 (CCNV).	40%
12.	Spanish Society for Medical Oncology, 2013 (SEOM).	32%
13.	European Society Medical Oncology, 2010 (ESMO).	30%
14.	Fagan et al., 2014 (FAGAN).	19%
15.	The Saskatchewan Cancer Agency, 2015 (SCA).	11%
	Mean \pm SD	58.7 \pm 28.5
	Median	75.0
	ICC	0.9

Acceptable quality score: (60%)

4.2.1.2 Complete AGREE II Appraisal

a) Domains' Scores

Based on an earlier assessment, eight guidelines that achieved the acceptable quality scores for the Domain Rigour of Development were further assessed using all AGREE II domains. Table 4.3 shows the domain scores for the eight guidelines. The mean quality scores across the six domains are modest in general, ranging from 48.9% to 83.1%. In particular, the mean score on the Rigour of Development Domain was the highest (83.11% \pm 6.8) with all guidelines exceeding 70% on this domain. Domain Applicability had the lowest mean score (48.9 \pm 25.7) and showed quality scores below 40% for four of the eight guidelines. The guidelines with the low quality scores on this

dimension were from VG, AHS, GCS and CCO. The low score on this domain reflected the lack in considering the facilitator, barrier and resource implication to its implementation by the guideline developers. The mean scores for the others domains were considered satisfactory: Scope and Purposes (68.8 \pm 16.8), Stakeholder Involvement (77.8 \pm 13.0), Clarity of Presentation (78.9% \pm 14.4) and Editorial Independence (70.5% \pm 22.7).

Examination of individual domain scores across the eight guidelines revealed that the quality scores were varied among the guidelines. Guidelines produced by the NCCN, BKCE and CCO had overall high performance in the complete AGREE II appraisal. The NCCN and BKCE scored higher than 60% in all six domains while CCO guideline had relatively high scores in all domains (>70%) except for the Applicability Domain (38%). The CCO guideline scored the highest for Domain Scope and Purpose (92%) and Domain Clarity of Presentation (94%). The SIGN guideline scored the highest for Domain Stakeholder Involvement (92%), Domain Rigour of Development (92%) and Domain Applicability (83%). The NCCN and AHS guidelines scored the highest for the Domain Editorial Independence (92%). However, four of the guidelines (VG, AHS, GSC and SIGN) had scores lower than 60% in two of the six domains. The NICE guidelines scored below 60 % for the Domain Scope and Purpose (56%).

The ICC values, which indicated the agreement between appraisers ranged from 0.74- 0.98. The inter-rater reliability was higher in the Domain Applicability (0.98) as compared to the other domains: Editorial Independence (0.89), Stakeholder involvement (0.88), Scope and Purposes (0.84), Clarity of Presentation (0.77) and Rigour of Development (0.74).

Table 4.3: Domain scores for complete AGREE II appraisal

No	Guidelines' developer	DOMAINS (%)					
		Domain Scope & purpose	Domain Stakeholder involvement	Domain Rigour of development	Domain Clarity of presentation	Domain Applicability	Domain Editorial Independence
1.	National Comprehensive Cancer Network (NCCN)	61	83	82	86	67	92
2.	Victoria Government (VG)	61	92	75	83	13	25
3.	Belgian Health Care Knowledge Centre (BKCE)	89	89	88	89	67	79
4.	Alberta Health Services (AHS)	83	58	77	64	23	92
5.	German Cancer Society (GCS)	61	69	76	56	31	63
6.	Cancer Care Ontario (CCO)	92	72	91	94	38	88
7.	Scottish Intercollegiate Guideline Network (SIGN)	47	92	92	92	83	58
8.	National Institute for Clinical Excellence (NICE)	56	67	84	67	69	67
Mean \pm SD (%)		68.8 \pm 16.8	77.8 \pm 13.0	83.1 \pm 6.7	78.9 \pm 14.4	48.9 \pm 25.7	70.5 \pm 22.7
Median (%)		61.0	77.5	83.0	84.5	52.5	73.0
ICC		0.84	0.88	0.74	0.77	0.98	0.89

b) Overall Guideline Assessment

This assessment component of the AGREE II instrument involved two global rating items, assessing the overall quality of the guideline and recommendation for its use in practice. Generally, no guideline was rejected by both appraisers. Overall quality scores ranged from 4.5 to the maximum of 6.5. The BKCE guideline achieved the highest

score, and the GSC guideline score was the lowest. Examination of the recommendations by appraisers for its use in practice showed complete agreement between appraisers in six of the guidelines. Both appraisers recommended the NCCN, VG, AHS, GSC, CCO and NICE guidelines to be used with modifications. The BKCE and SIGN guidelines were strongly recommended to be used without modifications by one of the appraisers while other appraiser recommended its use only after modifications. Overall quality scores and appraisers recommendations are shown in Table 4.4.

Table 4.4 Overall quality scores and recommendations by individual appraisers

No	Guidelines' developer	Overall quality scores (average)	Recommendations	
			Appraiser 1	Appraiser 2
1.	National Comprehensive Cancer Network	5.5.	Yes, with modifications	Yes, with modifications
2.	Victoria Government.	5	Yes, with modifications	Yes, with modifications
3.	Belgian Health Care Knowledge Centre.	6.5	Yes	Yes, with modifications
4.	Alberta Health Services.	5	Yes, with modifications	Yes, with modifications
5.	German Cancer Society.	4.5	Yes, with modifications	Yes, with modifications
6.	Cancer Care Ontario.	5.5	Yes, with modifications	Yes, with modifications
7.	Scottish Intercollegiate Guideline Network.	6	Yes, with modifications	Yes
8.	National Institute for Clinical Excellence.	5.5	Yes, with modifications	Yes, with modifications

c) Committee Review

Based on the data of the complete AGREE II appraisal, three guidelines including the NCCN, BKCE and SIGN were considered as good quality and were considered the most appropriate for adoption or adaptation in the development of Malaysian guidelines for oral cancer management.

The selection of the NCCN and BKCE guidelines were made on the basis of their overall high performance in all AGREE II domains. In addition, the BKCE guideline was strongly recommended for adoption by one of the appraisers. In terms of context and format of the guidelines, both guidelines clearly defined their scope and purpose. Both NCCN and BKCE guidelines provide comprehensive recommendations for diagnosis, treatment, and follow-up care of patients with oral cavity cancer. These guidelines were developed to assist all individuals who are involved in the decision making in cancer care including physicians, pharmacists, supportive healthcare provider, patients and their families, policy makers and many others.

The committee also decided to keep the SIGN's guidelines despite its low scores in Scope and Purpose (47%), and Editorial Independence (58%) domains because of the following reasons: 1) it scored high in the other four domains (>80%), 2) it guideline had the highest score for the Domains Stakeholder Involvement (92%), Rigour of Development (92%) and Applicability (83%), 3) it was strongly recommended to be used without modifications by one of the appraisers, 4) it's recommendations encompassing diagnosis, treatment and follow-up care which were clearly presented according to the supporting evidence.

Subsequently, three existing guidelines (NICE, GSC, VG) were excluded from further consideration, based on their low performance in the AGREE II appraisal. The CCO guideline was excluded in spite of its overall high performance in the complete AGREE II appraisal because the guideline adaptation concept has been applied in the development of this guideline. The AHS guideline was also excluded for the reason that the guideline was adopted from NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers, Version 1.2013 (National Comprehensive Cancer Network, 2013).

4.2.2 Assessment of Guideline: Currency

4.2.2.1 Guideline Currency Survey

The three selected guidelines (NCCN, BKCE, SIGN) were further assessed whether they are still current and relevant for the adaptation process. Table 4.5 indicates the guidelines currency assessment for the NCCN, BKCE and SIGN. All guidelines, except the SIGN guideline, were published after 2010. As compared to the SIGN guideline, the NCCN and BKCE guidelines included literature that had been published in the recent years. The literature search for the NCCN, BKCE and SIGN guidelines ranged from 1955-2014, 1980-2013 and 1967-2005 respectively. In terms of the guideline's update status, the NCCN guideline was updated annually, the BKCE guideline is the first and the most recent version and the SIGN guidelines had not been updated for ten years.

Results of the guideline currency survey revealed that at the time of the guideline development, the latest version of the NCCN guideline, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Head and Neck Cancers. Version 1.2016 (National Comprehensive Cancer Network, 2016) was available. The BKCE had no plans to update their guideline in the near future (the evaluation for an update is evaluated every year) as no new evidence was found that could invalidate any of the

recommendations comprising the BKCE's guideline. For the SIGN, they were aware of the new evidence during the peer review in 2011. However, they have no plans to update the guideline in the near future as it only involved a small part of the guideline's recommendations (section 3.2.1 and section 13 in the SIGN guideline).

4.2.2.2 Committee Review

Based on the result of guideline currency survey as discussed earlier, the research committee decided to retain all three guidelines for further evaluation. Both The NCCN and BKCE guidelines were considered current. However, the most current NCCN guideline version 1.2016 is used in this study instead of version 1.2015. The committee also retained the SIGN guideline, even though the guideline had not been updated since 2006 because of the inclusion of some guideline recommendations, particularly the follow-up care that other guidelines do not include. Some parts of the guidelines could be considered for adaptation for the Malaysian guidelines. Furthermore, the current peer review in 2011 indicated only minor update needed to the recommendations. It shows that the recommendations are quite current and still relevant to be used.

Table 4.5 Summary of the guideline currency assessment

No.	Survey Item	National Comprehensive Cancer Network (NCCN)	Belgian Health Care Knowledge Centre (BKCE)	Scottish Intercollegiate Guideline Network (SIGN)
1.	Publication Year	2015	2014	2006
2.	Total references	675	146	511
3.	Period cover by the literature.	1955-2014	1980-2013	1967-2005
	> 2000.	539 (79.9%)	138 (94.5%)	286 (52.9%)
4.	Guideline's update plans	Active NCCN guidelines are reviewed and updated at least annually.	Every 5 years or if important new evidence is available. (Evaluation for update is carried out annually).	Every 3 years.
5.	Clinical practice guideline last updated.	2016 (The latest version: 1.2016).	2014 (The first and most recent version).	Had not been updated since 2006. Peer review was carried out on 2011.
6.	Finding of guideline currency survey.	The updated version (1.2016) does not involve changing guideline's recommendation substantially. (minor changes in wording of the recommendations and update of some of the evidence).	No new evidence was found that could invalidate any of the recommendations comprising the guideline.	New evidence was found during the peer review on 2011. Only minor update needed 1. Section 3.2.1. Update on the role of Fine Needle Aspiration (FNA) in diagnosis of oral cancer. However, FNA is already recommended in the guideline, it would only be changing the evidence level supporting the recommendation. 2. Section 13. Involved oropharyngeal section in which it is beyond the scope of clinical area of interest.

4.2.3 Assessment of guideline: Clinical Content

Based on the earlier assessments (quality and currency assessments), the committee selected the most appropriate guidelines for adoption or adaptation as Malaysian guideline. The selected guidelines included:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Head and Neck Cancers. Version 1.2016 (National Comprehensive Cancer Network, 2016)-**NCCN**.
2. Oral cavity cancer: diagnosis, treatment and follow-up (Belgian Health Care Knowledge Centre, 2014a)- **BKCE**.
3. Diagnosis and management of head and neck cancer. A national clinical guideline (Scottish Intercollegiate Guidelines Network, 2006)- **SIGN**.

Following the PGEAC framework (Graham et al., 2003), the clinical contents of guideline recommendations in three selected guidelines were systematically assessed. The results of the assessment are illustrated below:

4.2.3.1 Summary of Recommendations in the NCCN, BKCE and SIGN

The summary of the recommendation in each guideline is tabulated in Table 4.6. A total of 192 recommendations were extracted from the three shortlisted guidelines and tabulated in a recommendation matrix (Appendix 5). The SIGN has the most number of recommendations (88) as compared to the BKCE (50) and NCCN (54) guidelines. The SIGN guideline consists of more recommendations with a high level of evidence (17%). Besides, the SIGN guideline consists of another component of evidence level, in which

33% the recommendations are based on the clinical experience of the guideline development group. This level of evidence is labelled as good practice points (GPP).

Table 4.6 Summary of recommendations in the NCCN, BKCE and SIGN guidelines

	Total	High level evidence	Low level evidence	GPP
NCCN	54	5 (9%)	49 (91%)	0
Diagnosis	9	0	9 (100%)	0
Treatment	36	5 (16%)	31 (84%)	0
Follow-up	9	0	9 (100%)	0
BKCE	50	2 (4%)	48 (96%)	0
Diagnosis	13	0	13 (100%)	0
Treatment	29	2 (7%)	27 (93%)	0
Follow-up	8	0	8 (100%)	0
SIGN	88	15 (17 %)	44 (52%)	29 (33%)
Diagnosis	13	0	12 (92%)	1 (8%)
Treatment	49	11 (22%)	17 (35%)	21 (43%)
Follow-up	26	4 (15%)	15 (58%)	7 (27%)
Total	192	22	141	29

4.2.3.2 Identification of Systematic Reviews on Oral Cancer Management

a. Literature Search to Identify Systematic Reviews

An additional search was conducted to identify relevant systematic reviews pertaining to the management of Oral Cancer in order to fill the gaps of the current evidence which is not covered by the selected guidelines. The search for recent systematic reviews yielded 214 potentially relevant articles. Of these, 203 articles were initially excluded based on titles and abstracts for the following reasons: i) articles could not be considered as systematic review, for example research protocol and summary of existing systematic reviews, (n= 21), ii) articles were not on oral cancer management (n=131), iii) the scope of the articles were beyond the clinical area of interest, for example, screening and prevention (n=32), iv) articles published before 2015 (n=13), and v) duplicates articles (n=6).

The remaining 11 articles were included for full-text review (Appendix G). After reviewing the full-text, another two articles were excluded because of the following reasons: i) review of current opinions (n=1) and ii) health technology assessment report (n=1). Finally, nine potential systematic reviews were considered relevant for an update of evidence pertaining to the management of oral cancer. Figure 4.2 illustrates the results of the systematic reviews selection process.

b. Characteristics of the Nine Shortlisted Systematic Reviews

Of the nine systematic reviews, two had been published in 2016 and seven had been published in 2015. The interventions covered by the systematic reviews are as follows:

- 1) swallowing exercise therapy (n=1),
- 2) induction chemotherapy (n=2),
- 3) chemoradiation therapy (n=1),
- 4) targeted therapy and immunotherapy (n=1),
- 5) diagnostic tests for Oral Cancer (n=3) and
- 6) Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG-PET)/CT for the detection of regional nodal metastasis (n=1).

The characteristics of the nine systematic reviews are documented in Table 4.7.

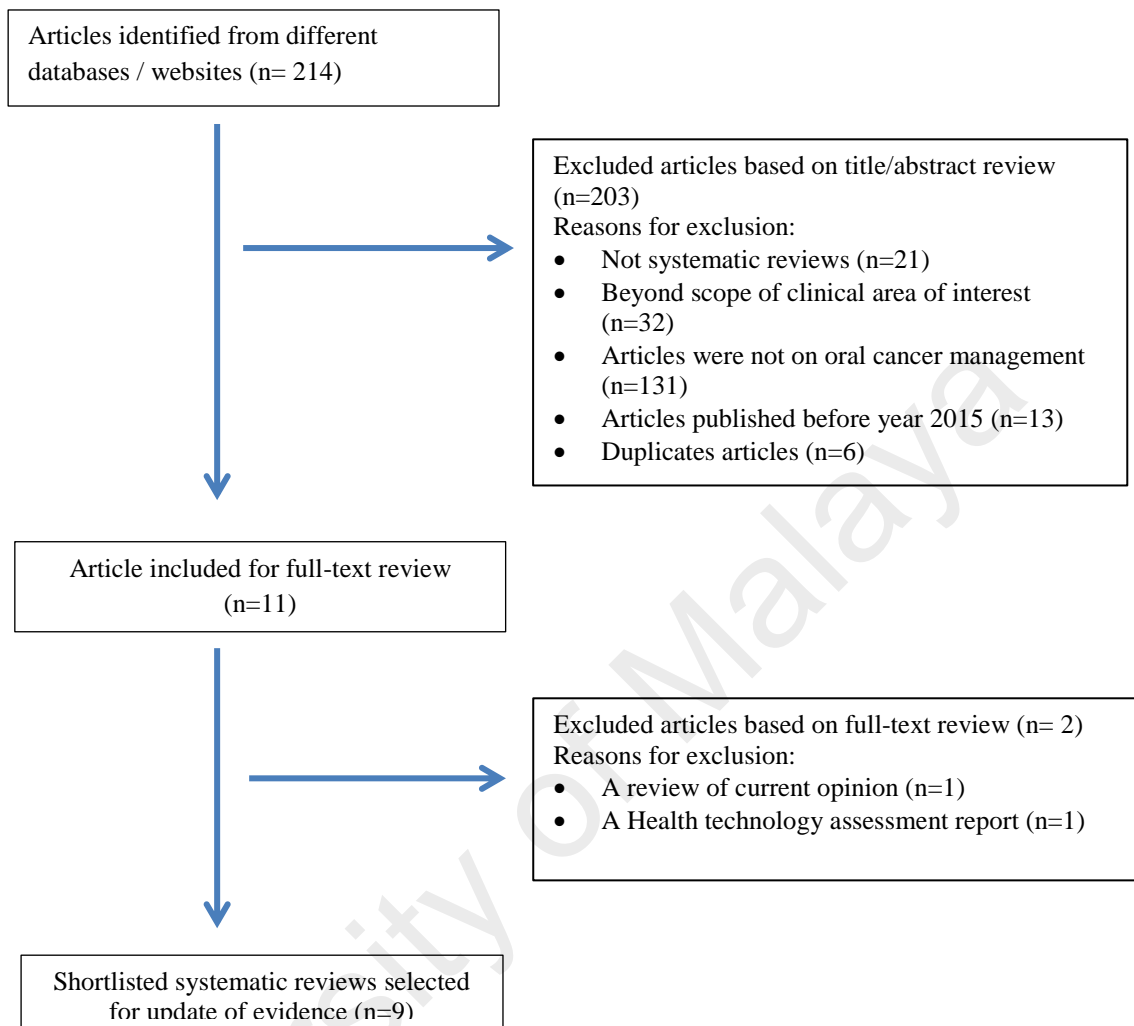


Figure 4.2 Results of the systematic reviews selection process

Table 4.7 Characteristics of the systematic reviews that were finally shortlisted

No.	Title	Author, Year	Journal Citation
1.	Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers.	Perry A, Lee SH, Cotton S, Kennedy C.,2016.	Cochrane Database of Systematic Reviews (Issue 8).
2.	Gemcitabine-Based Chemoradiation in the Treatment of Locally Advanced Head and Neck Cancer: Systematic Review of Literature and Meta-Analysis	Vanderveken Olivier M., Petr Szturz, Pol Specenier, Marco C. Merlano, Marco Benasso, Dirk Van Gestel, Kristien Wouters et al., 2016.	The oncologist, 21(1), 59-71.
3.	Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy.	Chan KKW, Glennly AM, Weldon JC, Furness S, Worthington HV, Wakeford H., 2015.	Cochrane Database of Systematic Reviews (Issue 12).
4.	Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions.	Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JLY, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C., 2015.	Cochrane Database of Systematic Reviews (Issue 5).
5.	Diagnostic capability of salivary biomarkers in the assessment of head and neck cancer: a systematic review and meta-analysis.	Guerra, Eliete Neves Silva, Ana Carolina Acevedo, André Ferreira Leite, David Gozal, Hélène Chardin, and Graziela De Luca Canto, 2015.	Oral oncology 51, no. 9
6.	Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis.	Marta, Gustavo N., Rachel Riera, Paolo Bossi, Lai-ping Zhong, Lisa Licitra, Cristiane R. Macedo, Gilberto de Castro, André L. Carvalho, William N. William, and Luis Paulo Kowalski, 2015.	European Journal of Cancer, 51(17), 2596-2603.
7.	Techniques for early diagnosis of oral squamous cell carcinoma: Systematic review.	Carreras-Torras, Clàudia, and Cosme Gay-Escoda, 2015.	Med Oral Patol Oral Cir Bucal, 20(3), e305-315.
8.	18 FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: a meta-analysis.	Sun, Rong, Xinye Tang, Yang Yang, and Cheng Zhang, 2015.	Oral oncology, 51(4), 314-320
9.	Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck: a meta-analysis.	Zhang, L., Jiang, N., Shi, Y., Li, S., Wang, P., & Zhao, Y., 2015.	Scientific Reports, 5

c. Committee Review

The information of all nine systematic reviews was summarised in evidence tables as shown in Appendix H. Of nine, three systematic reviews provide some evidence pertaining to the Oral Cancer management. Two of the systematic reviews indicated the effectiveness of tissue biopsy and histopathological examination for diagnosis of oral cancer (Carreras-Torras & Gay-Escoda, 2015; Macey et al., 2015) and one meta-analysis reported on good diagnostic performance showed by the FDG-PET/CT for detection of regional nodal metastasis in primary head and neck cancer patients (Sun et al., 2015). However, this evidence was not used to update any recommendation because tissue biopsy and histopathological examination, and FDG-PET/CT are already included in the recommendations on biopsy and imaging of neck lymph nodes respectively [see section 1.3 and section 1.6 in the recommendation matrix (Appendix E)].

The findings of the others six systematic reviews (Chan et al., 2015; Guerra et al., 2015; Marta et al., 2015; Zhang et al., 2015; Perry et al., 2016; Vanderveken et al., 2016) were inconclusive to support any update of the guidelines recommendations. As none of the systematic reviews identified by the literature search was used to update any of the recommendation, running the appraisal tool on these systematic reviews was deemed unnecessary. The decisions that had been made for each systematic review are recorded in Table 4.8.

Table 4.8 Decisions that had been made for each systematic review for update of evidence

No	Systematic reviews	Update of evidence		Reasons
		Yes	No	
1.	Perry A, Lee SH, Cotton S, Kennedy C. (2016). Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. <i>Cochrane Database of Systematic Reviews</i> , Issue 8.		√	The result is not statistically significant to support therapeutic exercises before, during and/or immediately after Head and Neck Cancer treatment in patients treated with advanced-stage oral cancer.
2.	(Vanderveken et al., 2016) et. al., (2016). Gemcitabine-Based Chemoradiation in the Treatment of Locally Advanced Head and Neck Cancer (LAHNC): Systematic Review of Literature and Meta-Analysis. <i>The oncologist</i> , 21(1), 59-71.		√	<p>The evidence was insufficient to enable a recommendation to be made for gemcitabine to be used as an alternative radio-sensitizer for Cisplatin-based concurrent chemoradiation (standard treatment) in patients with LAHNC in the Treatment of Locally Advanced Head and Neck Cancer.</p> <p><i>Despite its mild intrinsic toxicity, gemcitabine comes with high rates of severe mucositis when used in dosages exceeding 50mg/m²perweek. CCRT with low-dose gemcitabine provides a sufficient therapeutic ratio, combining clinical activity, similar to the higher-dose regimens, with lower toxicity. This seems to make it worth further investigation to improve the outcome in terms of efficacy and toxicity in order to reach a solid conclusion.</i></p>
3.	Chan KKW, Glenny AM, Weldon JC, Furness S, Worthington HV, Wakeford H. (2015). Interventions for the treatment of oral and oropharyngeal cancers: targeted therapy and immunotherapy. <i>Cochrane Database of Systematic Reviews</i> . Issue 12.		√	<p>The evidence was insufficient to enable a recommendation to be made on the use of targeted therapy and immunotherapy in combination with radiotherapy and chemotherapy for the treatment of oral cancer.</p> <p><i>1. Adding EGFR mAb to RT may increase overall survival progression-free survival and locoregional control, while resulting in an increase in skin toxicity for some mAb (cetuximab). However, the quality of evidence for both therapies are and high risk of bias respectively.</i></p> <p><i>2. The result is not statistically significant to support the use of tyrosine kinase inhibitors to standard therapies changes any of our primary outcomes.</i></p> <p><i>3. Very low quality evidence from a single study suggests that immunotherapy (rIL-2) combined with surgery may increase overall survival compared with surgery alone.</i></p>

“Table 4.8, Continued”

No	Systematic reviews	Update of evidence		Reasons
		Yes	No	
4.	Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JLY, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C. (2015). Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. <i>Cochrane Database of Systematic Reviews</i> , Issue 5.		√	The recommendation for the use of scalpel biopsy and histological assessment are already included in the guideline (see section 1.3 in the recommendation matrix [Appendix E]).
5.	Eliete Neves Silva Guerra, Ana Carolina Acevedo, Andrea Ferreira Leita, David Gozal, Helene Chardin, Graziela De Luca Canto. (2015). Diagnostic capability of salivary biomarkers in the assessment of head and neck cancer. A systematic review and meta-analysis. <i>Oral Oncol</i> , 1-14.		√	The evidence was insufficient (case-control studies) to enable a recommendation to be made on the use of salivary biomarkers in the diagnosis of head and neck cancer.
6.	Gustavo N. Marta, Rachel Riera, Paolo Bossi, Lai-ping Zhong, Lisa Licitra, Cristiane R. Macedo, Gilberto de Castro Junior, Andre L. Carvalho, William N. William Jr., Luis Paulo Kowalski. (2015). Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis. <i>European Journal of Cancer</i> , 51, 2596-2603.		√	The evidence was insufficient (only 2 studies included in the analysis), further validated using prospective trials were needed to support the use of induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients.
7.	Carreras-Torras, C., & Gay-Escoda, C. (2015). Techniques for early diagnosis of oral squamous cell carcinoma: Systematic review. <i>Medicina oral, patologia oral y cirugia bucal</i> , 20(3), e305.		√	The recommendation for the use of scalpel biopsy and histological assessment are already included in the guideline [see section 1.3 in the recommendation matrix (Appendix E)].
8.	Sun, R., Tang, X., Yang, Y., & Zhang, C. (2015). ¹⁸ F-FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer: a meta-analysis. <i>Oral oncology</i> , 51(4), 314-320.		√	FDG-PET/CT for the detection of regional nodal metastasis in patients with head and neck cancer is already included in the recommendation for imaging of neck lymph nodes [see section 1.6 in the recommendation matrix (Appendix E)]
9.	Zhang, L., Jiang, N., Shi, Y., Li, S., Wang, P., & Zhao, Y. (2015). Induction chemotherapy with concurrent chemoradiotherapy versus concurrent chemoradiotherapy for locally advanced squamous cell carcinoma of head and neck: a meta-analysis. <i>Scientific reports</i> , 5, 10798.		√	The finding did not support the use of IC followed by CCRT over CCRT alone for locally advanced squamous cell carcinoma of head and neck.

FDG-PET/CT: Fluorodeoxyglucose Positron emission tomography-computed tomography, IC: Induction Chemotherapy. CCRT: Chemoradiotherapy.

4.2.3.3 Assessment of the Guideline Recommendations

All members of the expert panel completed the individual assessment as required. The panel rating and comments based on independent assessments are shown in Appendix I, Appendix J and Appendix K:

1. Appendix I: Assessment form_National Comprehensive Cancer Network, 2016.
2. Appendix J: Assessment form_Belgian Health Care Knowledge Centre, 2014.
3. Appendix K: Assesment form_Scottish Intercollegiate Guideline Network, 2006.

Almost 60% of the 192 recommendations achieved 100% agreement. 10% of the recommendations were suggested to be excluded for the following reasons: the services are not widely available in this country such as FDG-PET/CT and Interstitial brachytherapy. A panel argued on the usefulness of the sentinel node biopsy in Malaysia for the reason that more than 50% of the patients were presented at late stage. The rest of the recommendations were accepted with modifications. The summary of the recommendations with 100% agreement is documented in Table 4.9.

Table 4.9 Summary of recommendations with 100% agreement

Guidelines	Total recommendations	100% agreement by the panel
NCCN	54	28 (52%)
BKCE	50	28 (56%)
SIGN	88	57 (65%)
Total	192	113 (58.9%)

4.3 Adopt or Adapt Guidelines for Local Use

4.3.1 Consensus on the Final List of Recommendations for the Malaysian Guideline

Based on the informal group discussion, the expert panel decided to adapt the three guidelines (NCCN, BKCE and SIGN) by accepting certain recommendations from the guidelines and combining them into a new local guideline. Of 192 total recommendations, the panel decided to accept 91 recommendations from the three shortlisted guidelines. Thirty three recommendations are from the BKCE guideline, 39 from the SIGN guideline and 19 from the NCCN guideline (Table 4.10). The BKCE has the most number of accepted recommendations for the diagnosis (n=10) and follow-up care (n=8), while the SIGN guideline has the most number of accepted recommendations for treatment (n=35). A total 81 recommendations were accepted by the panels without any modification, 10 recommendations were accepted with modifications and one recommendation was added to the conventional imaging of the primary tumour section. The decisions made by the expert panels are recorded in Appendix I, Appendix J and Appendix K accordingly.

Table 4.10: Distribution of the accepted recommendations according to the NCCN, BKCE and SIGN

Guideline	Panel Decision	Number of Recommendations			
		Diagnosis	Treatment	Follow-up care	Total
NCCN	Accepted	4	13	0	17
	Accepted (m)	0	2	0	2
BKCE	Accepted	7	13	8	28
	Accepted (m)	3	2	0	5
SIGN	Accepted	4	32	0	36
	Accepted (m)	0	3	0	3
Total		18	65	8	91

(m) = with modification

Of the 10 modified recommendations, three of the recommendations were modified based on the suggested evidence, one recommendation was modified based on expert opinion and six recommendations were combined into two recommendations. The details of the modified recommendations are illustrated in Table 4.11. The critical appraisals of the research evidence quality using the CASP appraisal tools are documented in Appendix P. The final list of the 88 recommendations that was agreed upon by the expert panel is presented in Table 4.12.

Table 4.11: Detailed of the modified recommendations

No.	Context	Source Guidelines	Modification made	References
1.3 (c)	Biopsy (see Appendix J)	BKCE	Modification based on current protocol from previous study. Prognostic factor, such as growing pattern (infiltrative vs. pushing border is changed to pattern of invasion (cohesive and non-cohesive) in the recommendation.	(Li et al., 2013; Almagush et al., 2015)
1.4	Conventional imaging of the primary tumour (see Appendix I)	NCCN	CT of the thorax, abdomen and pelvis was added to the recommendations.	(Arya et al., 2014)
1.8	Human Papillomavirus (HPV) Testing (see Appendix J)	BKCE	<i>Routine p16</i> testing was changed to <i>HPV testing</i> based on experts' opinion in order to exclude HPV18 testing subtype apart from HPV16 alone.	Expert opinion.
1.9.2	Primary site reporting (see Appendix J)	BKCE	Pattern of invasion was added as core reporting.	(Li et al., 2013; Almagush et al., 2015)
2.3.3 (g)	Advanced stage of oral cancer (Stage III and IV) (see Appendix K)	SIGN	Modification on the overall treatment time was made from <i>10-11 weeks</i> to <i>should not exceed 14 weeks</i> to suit with the local context.	(Rosenthal et al., 2002; Langendijk et al., 2010)
2.1	Multidisciplinary involvement. (see Appendix I, J, K)	NCCN, BKCE, SIGN	Three recommendations (1 recommendation from each guideline were combined into one recommendation) to suit with the local context.	Expert opinion.
2.2.1	Dental Evaluation (see Appendix I, J, K)	NCCN, BKCE, SIGN	Three recommendations (1 recommendation from each guideline were combined into one recommendation) to suit with the local context.	Expert opinion.

Table 4.12: The final list of the recommendations that was agreed upon by the expert panel

No.	Context	Recommendations	Level of evidence
<u>D)Diagnosis</u>			
1.1	Patient information and consultation.	<p>The patient must be kept fully informed about his condition, the treatment options and consequences. Information should be complete and communicated in a clear and unambiguous way. Patient preferences should be taken into account when deciding on a treatment option.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low
1.2	Clinical Examination	<p>The following investigation are recommended at diagnosis and staging of oral cancer:</p> <p>a. Complete head and neck exam, mirror and fiberoptic examination as clinically indicated.</p> <p>(Source: National Comprehensive Cancer Network, 2016).</p>	Low
1.3	Biopsy	<p>a. A biopsy should be taken from the most suspect part of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.</p> <p>b. When a patient with a diagnosis of oral squamous cell carcinoma is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical squamous cell carcinoma should be reviewed by an expert from a reference laboratory.</p> <p>c. The biopsy report should include: tumour localization, tumour histology, tumour grade, depth of invasion (if assessable), lymphatic, vascular and perineural invasion. Some other prognostic factors, such as pattern of invasion (cohesive and non-cohesive) can be considered.</p> <p>(Belgian Healthcare Centre, 2014; Li et al., 2013; Almagush et al., 2015).</p>	<p>Low</p> <p>Low</p> <p>Low</p>

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
1.4	Conventional imaging of the primary tumour	<p>The following investigation are recommended at diagnosis and staging of primary oral cancer:</p> <ul style="list-style-type: none"> a. Computerized tomography (CT) with contrast and/or magnetic resonance imaging (MRI) with contrast of primary as indicated. b. May consider CT of the thorax, abdomen and pelvis (TAP) if there are other lesions elsewhere. <p>(Source: National Comprehensive Cancer Network, 2016, Arya et al., 2014)</p>	<p>Low</p> <p>Low</p>
1.5	Imaging of locally advanced stage tumour	<ul style="list-style-type: none"> a. In patients presenting with cervical lymph node metastases, where CT or MRI does not demonstrate an obvious primary tumour, Fluorodeoxyglucose positron emission tomography - computed tomography (FDG-PET) should be performed as the next investigation of choice. b. In patients presenting with suspected recurrent head and neck cancer, where CT/MRI does not demonstrate a clear cut recurrence, FDG-PET should be performed as the next investigation of choice. <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>Low</p> <p>Low</p>
1.6	Imaging of neck lumps and nodes	<ul style="list-style-type: none"> a. CT or MRI from skull-base to sternoclavicular joints should be performed in all patients at the time of imaging the primary tumour to stage the neck for nodal metastatic disease. b. Where the nodal staging on CT or MRI is equivocal, Ultrasound guided fine needle aspiration (USFNA) and/or FDG-PET increase the accuracy of nodal staging. <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>Low</p> <p>Low</p>
1.7	Other staging interventions (identification of synchronous tumour and distant metastases)	<p>The following investigation are recommended at diagnosis and staging of oral cancer:</p> <ul style="list-style-type: none"> a. Chest imaging as clinically indicated. b. Examination under anaesthesia (EUA) with endoscopy, if indicated. c. Pre-anaesthesia studies as clinically indicated. <p>(Source: National Comprehensive Cancer Network, 2016).</p>	<p>Low</p>

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
1.8	Human Papillomavirus (HPV) Testing	<p>Due to insufficient evidence, routine HPV testing is not recommended in patients with oral cavity cancer. In patients without any of the common risk factors (e.g. smoking, alcohol abuse) for oral cavity cancer, HPV testing is recommended although there is no evidence at present that it alters treatment decisions in these patients.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014; expert’s opinion)</p>	Low
1.9 Histopathology.			
1.9.1	Resection margin	<p>a. To avoid a positive resection margin (which is associated with a poorer prognosis), frozen sections taken intraoperatively may be useful.</p> <p>b. A distance of at least 10 mm from the palpable tumour margin, whenever technically or anatomically possible, should be taken as a guide for resection to allow a minimal distance of 3-5 mm from the margin of the resected tissue to the primary tumour in the formalin-fixed specimen.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low Low
1.9.2	Primary site reporting.	<p>For discussion with the clinician, the histopathological findings must describe the exact localization of any existing R+ status. The anatomical topography must be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding.</p> <p>The histopathological result must include:</p> <ul style="list-style-type: none"> • tumour localization, • macroscopic tumour size, • histological tumour type, • histological tumour grade, • depth of invasion, • pattern of invasion, • lymphatic, • vascular and perineural invasion, • locally infiltrated structures, • pT classification, • details of affected areas and infiltrated structures, • R status and p16 (if not done on biopsy). <p>(Belgian Healthcare Centre, 2014; Li et al., 2013; Almangush et al., 2015).</p>	Low

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
1.9.3	Neck and metastatic disease reporting.	<p>The histopathological findings from a neck dissection specimen must describe:</p> <ul style="list-style-type: none"> • the anatomical topography, • the side of the neck, • type of neck dissection, • eliminated levels, • total number of lymph nodes plus number of lymph nodes affected, • number of lymph nodes per level, • level of the affected lymph nodes, • diameter of the largest tumour deposit, • additionally removed structures, • extracapsular spread (if present). • <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low
<u>2)Treatment</u>			
2.1 Multidisciplinary involvement			
2.1	Multidisciplinary involvement	<p>a. Treatment plans should be formulated by a multidisciplinary team (core members and non-core member) in consultation with the patients and family member.</p> <p>The core members comprise the specialist disciplines of:</p> <ul style="list-style-type: none"> • oral and maxillofacial surgery, • otorhinolaryngology, • pathology, • clinical oncology, • pathology, • radiology, • plastic and reconstructive surgery. <p>The non-core members comprise of:</p> <ul style="list-style-type: none"> • general practitioner, • dentist, • nursing care, • speech and swallowing therapist, • nutritional therapist, • psychosocial worker, <p>b. Individual patient characteristics, local expertise and patient preference should guide management of oral cancer.</p> <p>(Source: National Comprehensive Cancer Network, 2016; Belgian Health Care Knowledge Centre, 2014; Scottish Intercollegiate Guideline Network, 2006).</p>	<p>Low</p> <p>GPP</p>

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
2.2 Pre-treatment assessments.			
2.2.1	Dental evaluation	<p>Patients with head and neck cancer, especially those planned for resection of oral cancers or whose teeth are to be included in a radiotherapy field, should have the opportunity for a dental or prosthodontics evaluation by an appropriately experienced dental practitioner. The evaluation should include panoramic oral radiograph (OPG), risk assessment of caries and periodontal. The dental practitioner should give preventive advice and perform necessary restorative or prosthodontic work.</p> <p>(Source: National Comprehensive Cancer Network, 2016; Belgian Health Care Knowledge Centre, 2014; Scottish Intercollegiate Guideline Network, 2006).</p>	Low
2.2.2	Nutritional, speech and swallowing evaluation.	<p>Nutrition, speech, and swallowing evaluation/therapy before and after treatment as indicated and should involve a registered dietitian and a speech-language/swallowing therapist.</p> <p>(Source: National Comprehensive Cancer Network, 2016).</p>	Low
2.3 Treatment of primary non-metastatic oral cancer.			
2.3.1	General recommendations	<p>Factors to be considered in treatment plan:</p> <ol style="list-style-type: none"> a. Management of early oral cavity tumours should be individualised for each patient. b. Decisions regarding the choice of primary treatment modality should be made in consultation with the patient and the family, and should take into account the anatomical location of the tumour and availability of local expertise. c. In those patients where surgical resection is possible, the likelihood of obtaining adequate surgical margins with acceptable morbidity, functional outcome and quality of life must be considered. d. The likely short and long term morbidity resulting from radiotherapy must be considered. <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>GPP</p> <p>GPP</p> <p>GPP</p> <p>GPP</p>

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
2.3.2	Early stage of oral cancer (Stage I and Stage II)	a. Provided the patient's general condition permits it and the oral cavity carcinoma can be curatively resected, surgical resection of the tumour should be performed and followed by immediate reconstruction, when required.	Low
		b. In case of a microscopically residual tumour (R1 resection), targeted follow-up resection should ensue with the aim of improving the patient's prognosis, whenever possible.	Low
		c. Continuity of the mandible should be preserved on tumour resection or restored post-resection, provided no radiological or intraoperative evidence has been found of tumour invasion of the bone.	Low
		d. Reconstructive measures should from the onset be integrated in the surgical approach. When planning reconstruction, consideration must be given to the entire oncological scenario. The anticipated functional or cosmetic improvement must justify the efforts involved in reconstruction.	Low
		(Source: Belgian Health Care Knowledge Centre, 2014).	
		e. Definitive radiotherapy (RT) may be offered to early stage patients (T1-2, N0) who are medically inoperable or refuse surgery. Patients who go on to develop residual disease after definitive RT should be considered for surgery.	Low
		(Source: National Comprehensive Cancer Network 2016).	
		f. Interstitial brachytherapy may be offered to early stage patients. The treatment should be performed by experienced teams in centres with adequate radiation protection facilities.	Low
		g. Re-resection should be considered to achieve clear histological margins if the initial resection has positive surgical margins.	Low
		h. If re-resection is not possible, postoperative radiotherapy should be considered.	GPP
i. Postoperative radiotherapy should be considered for patients with clinical and pathological features that indicate a high risk of recurrence.	Low		
j. Administration of chemotherapy (CRT) concurrently with postoperative radiotherapy should be considered, particularly in patients with extracapsular spread and/or positive surgical margins. (Source: Scottish Intercollegiate Guideline Network, 2006).	High		

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
2.3.3	Advanced stage of oral cancer (Stage III and IV)	<p>a. Patients with resectable disease who are fit for surgery should have surgical resection with reconstruction. (Source: Scottish Intercollegiate Guideline Network, 2006).</p>	Low
		<p>b. The decision to perform surgery must be made on the basis of the ability to achieve tumour-free resection margins and postoperative quality of life. For locally advanced tumours, the postoperative functional consequences need to be prospectively and carefully assessed. For instance, when a total glossectomy (+/- total laryngectomy) is the only oncologically suitable surgical option, non-surgical organ preservation protocols must be seriously considered. (Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low
		<p>c. Radical external beam radiotherapy with concurrent chemotherapy should be considered when:</p> <ul style="list-style-type: none"> • the tumour cannot be adequately resected. • the patient’s general condition precludes surgery. • the patient does not wish to undergo surgical resection. 	High
		<p>d. Postoperative radiotherapy should be considered for patients with clinical and pathological features that indicate a high risk of recurrence. (Source: Scottish Intercollegiate Guideline Network, 2006).</p>	Low
		<p>e. Postoperative radiotherapy should be performed for advanced T categories (T3/T4), close (< 4 mm) or positive resection margins, tumour thickness > 10 mm, lymph node involvement (> pN1) and extra-capsular rupture/soft tissue infiltration. It should be considered for peri-neural extension or lymphatic vessels infiltration. For high-risk patients (e.g. close or positive resection margins, extracapsular spread) administration of chemotherapy concurrently with postoperative radiotherapy can be considered, (Source: Belgian Health Care Knowledge Centre, 2014).</p>	High
		<p>f. Interrupting and prolonging a course of radical radiotherapy should be avoided.</p>	Low
		<p>g. Overall estimated treatment time from surgery to completion of radiotherapy should not exceed 14 weeks in the absence of postoperative medical or surgical complications. (Source: Scottish Intercollegiate Guideline Network, 2006, Langendijk et al., 2010, Rosenthal et al., 2002)</p>	Low

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
2.3.3	Advanced oral cavity cancer (Stage III and IV) Continue.	<p>h. Concurrent chemoradiotherapy should only be administered where there are appropriate facilities for monitoring toxicity, with rapid access to appropriate outpatient and inpatient support for the treatment of acute radiotherapy and chemotherapy toxicity.</p> <p>i. The routine use of neo-adjuvant chemotherapy in oral cavity cancer is not recommended.</p> <p>(Source: (Scottish Intercollegiate Guidelines Network, 2006).</p>	<p>High</p> <p>High</p>
2.3.4	Management of the neck lymph nodes.	<p>a. Management of the neck lymph nodes should follow the same treatment principles as those applied for the primary tumour (e.g. if the primary tumour is surgically treated, a neck dissection should be performed).</p> <p>b. Perform a selective neck dissection of at least level I, II and III in all patients with a cN0M0 oral cavity SCC that is treated surgically.</p> <p>c. A neck dissection can be omitted exceptionally in some patients with a cT1N0M0 oral cavity SCC, depending on the localisation and thickness of the tumour.</p> <p>d. Perform a selective ipsilateral neck dissection of at least level I, II, III and IV with – if oncologically feasible – preservation of the sternocleidomastoid muscle, jugular vein and spinal accessory nerve in all patients with a cN+M0 oral cavity SCC that is treated surgically.</p> <p>e. Consider a contralateral neck dissection in patients with a non-metastatic oral cavity SCC that is at or crossing the midline or not clearly localized laterally.</p> <p>f. Consider performing a diagnostic evaluation of the neck with conventional imaging techniques (CT or MRI) or PET/CT three to six months after completion of primary (chemo) radiotherapy.</p> <p>g. In patients with oral cavity cancer (N1-3) and complete response to chemoradiotherapy (assessed by FDGPET/CT, CT or MRI), there is no data to support an additional lymph node dissection.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	<p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p>

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
2.4 Treatment of very advanced-stage oral cancer (M0) T4b, any N or unresectable nodal disease or unfit for surgery.			
		<p>a. Participation in clinical trials is preferred for all patients with very advanced cancers.</p> <p>b. Patients should undergo standard therapy based on their PS = Performance Status (Eastern Cooperative Oncology Group [ECOG]).</p> <p>c. For patients with a PS of 0 or 1, the standard treatment is concurrent chemotherapy and radiotherapy. Other options are induction chemotherapy followed by RT or chemotherapy/RT.</p> <p>d. PS 0-2: Definitive RT with or without concurrent chemotherapy.</p> <p>e. PS 0-3: Palliative RT or single-agent chemotherapy or best supportive care.</p> <p>f. Perform neck dissection following the above treatment (if feasible) in the instance of residual neck disease and primary site are controlled.</p> <p>(Source: National Comprehensive Cancer Network, 2016).</p>	<p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p> <p>Low</p>
2.5 Treatment of locoregional recurrence disease.			
2.5.1	General evaluation.	<p>a. Decisions regarding the appropriate management of a locoregional recurrence of head and neck cancer should be made on an individual basis taking into account:</p> <ul style="list-style-type: none"> • The stage of recurrent tumour and its potential resectability. • Previous treatment • Likely treatment efficacy • Likely treatment-related morbidity and functional outcome and consequent effects on quality of life • patient’s general health • patient’s wishes. <p>b. Decisions regarding the management of locoregional recurrence of head and neck cancer should be made by the multidisciplinary team in consultation with the patient following histological confirmation of recurrence and full restaging (clinical and radiological).</p> <p>c. Patients and their relatives/carers should be carefully counselled about the likely outcome of surgical and radiotherapeutic salvage, with respect to survival, risk of treatment-related morbidity and mortality, and likely resulting quality of life.</p> <p>d. Early referral to palliative care for symptom control should be considered.</p> <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>GPP</p> <p>GPP</p> <p>GPP</p> <p>GPP</p>

“Table 4.12 continued”

No	Context	Recommendations	Level of evidence
2.5.2	Resectable locoregional recurrence	<p>a. Surgery is recommended for resectable recurrent or persistent locoregional disease.</p> <p>b. For patients with resected oral cavity cancers who have the adverse features of extracapsular nodal spread and/or positive margin and the patients did not have prior RT the treatment is postoperative chemotherapy/RT.</p> <p>c. For patients with resected oral cavity cancers and who have other risk features such as pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, or vascular tumor embolism and the patients did not have prior RT, the options include RT or consider chemotherapy/RT.</p> <p>d. For patients with resected oral cavity cancers with prior RT, the options include surgery with or without postoperative reirradiation or chemotherapy/RT.</p> <p>e. Enrollment in a clinical trial can be considered.</p> <p>(Source: National Comprehensive Cancer Network, 2016).</p>	<p>Low</p> <p>High</p> <p>Low</p> <p>Low</p> <p>Low</p>
2.5.3	Unresectable locoregional recurrence	<p>a. If the recurrence is unresectable and the patients did not have prior RT, then RT with concurrent chemotherapy is recommended, depending on the PS.</p> <p>b. If the recurrence is unresectable and the patients have prior RT, the treatment option include reirradiation with or without chemotherapy, or chemotherapy alone.</p> <p>(Source: National Comprehensive Cancer Network, 2016).</p> <p>c. Patients with small accessible recurrences in a previously irradiated region may be considered for interstitial brachytherapy in centres with appropriate facilities and expertise.</p> <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>Low</p> <p>Low</p> <p>Low</p>

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
2.6 Treatment of metastatic or recurrent disease not eligible for curative treatment.			
2.6.1	General recommendation	<p>a. The care of patients with incurable head and neck cancer should be managed by the palliative care services in conjunction with the multidisciplinary team.</p> <p>b. All modalities of therapy should be considered as options for the palliation of head and neck cancer.</p> <p>c. Short term toxicity and length of hospital stay should be balanced against likely symptomatic relief.</p> <p>d. A documented pathway of care should be discussed and agreed with the patient, relatives, carers and general practitioner.</p> <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>GPP</p> <p>GPP</p> <p>GPP</p> <p>GPP</p>
2.6.2	Palliative chemotherapy	<p>a. Patients of adequate performance status should be considered for palliative chemotherapy which may reduce tumour volume.</p> <p>b. Single agent methotrexate, single agent cisplatin, or cisplatin/5Fu combination should be considered for palliative chemotherapy in patients with head and neck cancer.</p> <p>c. A excessive toxicity from intensive chemotherapeutic combination regimens should be avoided.</p> <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	<p>High</p> <p>High</p> <p>High</p>
2.6.3	Palliative radiotherapy	<p>Radiotherapy may be considered for palliative treatment in patients with locally advanced incurable head and neck cancer.</p> <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	Low
2.6.4	Palliative surgery	<p>Appropriate surgical procedures should be considered for palliation of particular symptoms, taking local expertise into consideration.</p> <p>(Source: Scottish Intercollegiate Guideline Network, 2006).</p>	GPP

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
<u>3) Follow-up care.</u>			
3.1	Clinical and imaging evaluation	<p>An individually structured follow-up schedule should be devised for each patient. The quality of life, side effects of treatment, nutritional status, speech, dental status, thyroid function, smoking and alcohol consumption, etc. should be surveyed periodically. There is no evidence to support routine use of imaging techniques for the detection of locoregional or metastatic recurrence during follow-up. Follow-up frequency, even in symptom-free individuals, should be at least every 3 months in the first and second year, every 6 months in the third to fifth year, and annually afterwards.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low
3.2	Dental rehabilitation	<p>a. In patients having undergone surgery and/or irradiation for carcinoma of the oral cavity, the masticatory function should be restored with the help of functional masticatory rehabilitation, using conventional prosthetics and/or implants. Surgical interventions (e.g. extractions) should be performed by professionals with experience in treating patients with head and neck cancer. The patients should undergo routine dental check-ups at a frequency depending on the individual patient case (usually every 4-6 months).</p> <p>b. Infected osteoradionecrosis of the jaw is a serious treatment complication that should be managed in specialized centres.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low
3.3	Speech and swallowing rehabilitation.	<p>a. Patients with chewing, speaking and swallowing problems should be timely provided with appropriate functional therapy. The patients should be introduced to suitably qualified therapists prior to commencing treatment if the scheduled surgical or conservative procedures (e.g. radiotherapy) are likely to cause problems with chewing, swallowing and/or speech.</p> <p>b. Patients with dysphagia should undergo appropriate diagnostic procedures, e.g. clinical exam by the speech therapist, videofluoroscopy or fiber-optic endoscopy.</p> <p>(Source: Belgian Health Care Knowledge Centre, 2014).</p>	Low

“Table 4.12 continued”

No.	Context	Recommendations	Level of evidence
3.3	Speech and swallowing rehabilitation. Continue.	a. Patients having eating and speaking problems due to carcinoma of the oral cavity and/or its management should have access to speech therapists and nutritional therapists with experience of such pathologies before, during and after treatment. (Source: Belgian Health Care Knowledge Centre, 2014).	Low
3.4	Nutritional therapy	Patients should be regularly screened for malnutrition due to oral cavity cancer or its treatment. Patients at risk for malnutrition should receive timely and on-going professional dietary counselling and nutritional therapy. (Source: Belgian Health Care Knowledge Centre, 2014).	Low
3.5	Psychosocial counselling and support	Patients with oral cavity cancer (and their family, carers) should be offered dedicated psychosocial support on a continuous basis within the context of a multidisciplinary team. (Source: Belgian Health Care Knowledge Centre, 2014).	Low

4.3.2 The Draft Guideline

The draft guideline was prepared by the researcher based on the final list of recommendation as documented in Table 4.12. It consisted of three sections namely: 1) Introduction, 2) Development of the guideline and 3) Clinical Recommendations with a total of 48 pages. The first section contains a brief description on the burden of the condition, the rationale for the guideline development, the objective for developing the guideline, target population and target user of the guideline. The second section provides detailed information on the process involved in the guideline development. The third section is the main section which outlines the 88 clinical recommendations along with its sources and the corresponding level of supporting evidence. The clinical

recommendations were divided into three subsections namely: 1) diagnosis, 2) treatment, and 3) follow-up care. The summary of the evidence used to develop the guideline recommendations is also presented in this section. The algorithm for the management of oral cancer is placed at the front section of the guideline. The detailed description of each section is illustrated in Table 3.6.

4.4 Multidisciplinary Specialists Feedback

The data were collected from one Focus Group Discussions (FGD). Twelve potential participants were invited to take part in the FGD). Of the twelve invited participants, nine agreed to participate in the FGD. The other three were unable to do so because of prior work commitments. On the day of the FGD, a total of seven specialists comprising four Oral Maxillofacial Surgeons, one Oral Medicine and Oral Pathologist, and one Senior Dental Public Health Specialist participated in the FGD. The other two were unable to attend the FGD as they were taken ill on that day. The meeting was also attended by the supervisors of the research project. The participants' comments and feedback are presented as follows:

4.4.1 Format of the guideline

4.4.2 Content of Section 1 (Introduction) and Section 2 (Development of the Guideline).

4.4.3 Content of Section 3 (Clinical Recommendations)

4.4.4 Algorithm

4.4.5 Clinical Audit Indicators

4.4.6 Concerns of the specialists

4.4.1 Format of the Guideline

Participants were asked for general feedback regarding the format of the guideline. Generally, they gave positive feedback on the overall structure of the draft guideline. One participant stated that the draft was comprehensive, well organised and he found that the content was easy to read. Verbatim of the participant is displayed in Table 4.13.

Table 4.13: Participant's comment regarding the format of the guideline

Participant	Verbatim
Participant 3	"I think it is Ok, easy flow, correct flow, easy to read, all required information is there".

4.4.2 Section 1 (Introduction) and Section 2 (Development of the Guideline)

In reviewing these sections, a participant asked whether resource implication is mentioned in the guidelines. An explanation was given that the implementation of the guideline would not require any additional resources because this guideline is meant to be adapted in the Malaysian system based on the existing resources available. Therefore this information is not mentioned in the draft guideline. The participant also mentioned about the spelling medical *judgment* in the target users' statement that needs to be corrected. Lastly, another participant suggested Otorhinolaryngologists need be added to the target users of the guideline apart from Head and Surgeons and the suggestion was accepted by the others. In the new version of the draft guideline, the correction was made based on participants' comments. Verbatim of the participants are displayed in Table 4.14.

Table 4.14: Participants' comments regarding the content of Section 1 (Introduction) and Section 2 (Development of the Guideline)

Participant	Verbatim
Participant 4	"Is resource implication mentioned here in the guideline?"
Participant 7	"I don't see the ORL there. Head and Neck Surgeon are actually not only ORL. They are also General Surgeons, who are Head and Neck Surgeon. It is a bit ambiguous. So we need to put the Otorhinolaryngologist as one of the target users of the guideline. Just add ORL after the Head and Neck Surgeons."
Participant 4	"The spelling of the medical <i>judgment</i> in the second paragraph of target users statement needs to be corrected."

4.4.3 Section 3 (Clinical Recommendations)

The clinical recommendations section is the main part of the guideline. The participants spent a substantial amount of time discussing this section. Participants' feedback on the clinical recommendations are presented in two parts including:

4.4.3.1 Clinical recommendations (diagnosis, treatment and follow-up care).

4.4.3.2 Summary of the evidence.

4.4.3.1 Clinical Recommendations

Generally, participants accepted most of the 88 recommendations (please refer Table 4.12 for the numbering of the recommendations), but had specific comments about the contents of some recommendations as follows:

1) Diagnosis

a. Recommendation 1.1: Patient information and consultation.

b. Recommendation 1.3: Biopsy [1.3 (a) and 1.3 (b)].

c. Recommendation 1.5: Imaging of locally advanced stage tumour.

d. Recommendation 1.9.2: Primary site reporting.

a. Recommendation 1.1: Patient Information and Consultation

It was recommended that the patient must be fully informed about his condition, the treatments options, and consequences. However, the participants stated that they had trouble informing the patients about their condition because some family members prevented them from breaking the bad news to the patients especially if they were their elderly parents. One of the participants said that he would acknowledge what had been requested by the family members. However, other participants believed that the patient needs to be informed about their diagnosis prior to proceeding with the treatment. Participants also stressed the importance of family support because some patients were not taken care of after surgery. A participant felt that this issue needs to be addressed in the guideline because it has some important impact on patient's survival. As a result of the discussion, it was decided and agreed upon that this issue can be handled when discussing the treatment plan with the family members or inserting a statement in the document for surgery, for example, the consent form rather than in this guideline. Therefore, it was agreed by the participants that the recommendation remained as it is.

Verbatim of the participants are displayed in Table 4.15.

Table 4.15: Participant's comments regarding the patient information and consultation

Participant	Verbatim
Participant 2	“Some family members or relatives came directly to us and asked not to reveal the diagnosis. When I asked somebody in medico-legal about this matter, they suggested us to acknowledge what was requested by the family members. This is what I am saying whether we want to adopt or adapt this recommendation because in the Western Countries, patients must know.”

“Table 4.15 continued”

Participant	Verbatim
Participant 3	“Sometimes, if the treatment is aggressive and will involve deformity in form and functions, it is not fair for the patients not to know. For the consent and everything. Sometimes, we have to negotiate with the family members. Unless the patient need palliative treatment. That one is ok if we do not tell the patients.”
Participant 2	“This is what we deal with the family member. Yes, we would not tell, but if something goes wrong in the end you will still need to tell.”
Participant 1	“We have a lot of problems with this issue. Family members usually came to me and said I don’t want my father or mother to know about his or her condition. I have my own principle. For me to proceed with the treatments, the patient needs to be informed, even they are an immediate family member. They have to understand because patients are the one that is going to suffer or to be treated. I will never do surgery for patients with no social support.”
Participant 3	“That is a major issue in this part of the world. I don’t know whether it is advised to put it in this guideline or not-the support from the family - because there are a lot of irresponsible family members here. Should we put a recommendation that <i>if there is no family support, the destructive procedure should not be carried out</i> ? The patient will suffer or otherwise social worker should be there.”
Participant 2	“If say, we let the patients go on with the disease, he may die within a year. However, without the family support, they may die in six months.”
Participant 1	“I agreed. In Sabah, we have a lot of patients, initially, the family members said, they will take care of their parents. After surgery, nobody takes care of the patients.”

b. Recommendation 1.3: Biopsy

Recommendation 1.3 (a)

One participant brought up the issue of inconclusive diagnosis and asked for further explanation on how to manage those cases. Two participants had different opinions of which the first participant stated that if the result is inconclusive, but the malignancy is suspected, the biopsy needs to be repeated while the second participant suggested removal of the tumour if the surgery does not cause any deformity in form and function. However, it was agreed upon that patient preferences should be taken into account when deciding the treatment plan. The pathologist emphasized that adequate tissue should be

taken at the location during the biopsy with adequate depth of tumour excised in order to get accurate histopathological results. Lastly, another participant suggested the term *suspect part* is changed to *suspected part(s)* because the biopsy of few parts is done in certain occasions.

Recommendation 1.3 (b)

A participant requested clarification on the recommendation 1.3 (b): *When a patient with a diagnosis of oral squamous cell carcinoma is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre.* Some participants noted a discrepancy between what is recommended and their current practice. They thought that second report is not necessary as long as it is issued by a gazetted specialist while some of them did ask for another diagnosis confirmation in certain occasions. Finally, they agreed that it cannot be done routinely and only applied to certain occasions or upon request, particularly if the pathology and clinical findings do not match.

Consequently, participants accepted both the recommendations without any changes except for highlighting the word **upon request** for 1.3 (b) as they realised that the statement was already mentioned in the recommendations. Verbatim of the participants are displayed in Table 4.16.

4.16: Participants' comments regarding the recommendations on biopsy

Participant	Verbatim
Recommendation 1.3(a)	
Participant 1	“I think the word suspect part in the In 1.3 (a) Biopsy should be suspected part(s). Sometimes, we biopsy few parts.”
Participant 2	“Did any of the recommendations talked anything about an inconclusive diagnosis? It does effect on how we are going to manage the case especially for resectable cases.”
Participant 3	“When it is not matched, I will see the biopsy. Tumour invading here and then, and you said benign. Normally, I always write to rule out the malignancy. When the Pathologist said that, malignancy cannot be rule out, you have to repeat the biopsy.”
Participant 6	“We have to find out exactly where you took biopsy because where you took the biopsy may not where the tumour is.”
Participant 6	“The report can only come back as being malignant if you have given us the full depth which is not possible to do sometimes or when it is a keratotic lesion. That is why the patient had had up to 3-4 biopsies on something that looked very suspect. The Pathologist just cannot reveal any malignancy because histologically it does not fit the criteria.
Participant 5	“Or you can remove if the surgery does not lead to any compromised in form and function. Obviously, we have to explain to the patient and it is recorded in our card. I have an inconclusive biopsy, you want me to remove it, re-biopsy or you want just to observe.”
Recommendation 1.3(b)	
Participant 6	“So far we never send any slices or block away and it is always just putting in the report that we gave. I mean, ideally, it would be the best thing. Would that mean the delay in the management of the patient?”
Participant 6	“If we considered the whole of the Ministry of Health as one institution, that’s not the issue. You just use the report that is issued by a MOH facility. If it was the other way round. If the patient goes to UMMC and the report was written by a MOH residency. The UMMC would have to insist the report is issued by the UMMC Pathologist.”
Participant 7	“My opinion, if the Pathologist from UMMC or Pathologist from Ministry of Health as long as the Pathologist is gazetted as a specialist, I will accept the report and would not ask for another one.”
Participant 2	“So, the practice now, the patients can be referred from anywhere. As long as it has been read by a gazetted specialist, it will be accepted.”
Participant 5	“Sometimes, your pathology result, clinically it does not indicate malignancy and the report came back as malignancy. Before you plan to treat the patient, you may need another confirmation.”
Participant 6	“We can put it in but it is not the current practice. I am wondering now about the billing. Who is going to pay for this second report?”
Participant 3	“There are occasions, where the pathology and clinical findings do not tally or are not in line. I mean suspicious. I asked for the block. It cannot be routine, I think put ‘upon request’.”

c. Recommendation 1.5: Imaging for Locally Advanced Stage Tumour

As FGD-PET scan is not widely available in the country, participants suggested that the words *whenever possible* should be added in the recommendation. Therefore, FGD-PET would be indicated for certain cases only if the result of CT or MRI is inconclusive in detecting a recurrent tumour. Verbatim of the participants are displayed in Table 4.17.

Table 4.17 Participants' comments regarding the imaging for locally advanced

Participant	Verbatim
Participant 3	"I want to touch about the PET scan. We know our country only has 3 PET scans. Are we going to put this recommendation or not? For example, we have tumours in Kelantan or somewhere else. If CT or MRI is inconclusive, definitely it is mandatory that you have to do PET scan."
Participant 2	"Can we add <i>whenever possible</i> at the end of the recommendation, so it is not mandatory for every case."
Participant 3	"I agree that PET scan has a reliable role in the monitoring of occult recurrence. The statement here is quite good and we add 'whenever possible'."

d. Recommendation 1.9.2: Primary Site Reporting

While discussing on the data to be reported in the histopathological result, the pathologist suggested the minimum dataset required for histopathology reporting as what has been recommended by The Royal College of Pathologists. Another participant stressed the importance of marking when sending an excised specimen to the Pathologist. In reviewing the recommendation, they realised that both information has been covered in the recommendations. Due to insufficient evidence, they agreed to omit P16 and R status from the list of the histopathological report. R status is not something that can be ruled-out from the pathology examination besides tumour margin. Therefore, the statement on *exact localization of any existing R⁺ status* in the second

row was suggested to be replaced with *exact tumour margin* by the participants.

Verbatim of the participants are displayed in Table 4.18.

Table 4.18 Participants' comments regarding the primary site reporting

Participant	Verbatim
Participant 6	"What I can give you is what is recommended by The Royal College of Pathologists. There is a minimum data set that is required for the reporting of excised specimens."
Participant 6	"P16 is something that is not done in any of our laboratories. So, that is something that we are not reporting unless there is evidence that says why the P16 has to be done. In the HPV recommendations, it is already stated <i>that due to insufficient evidence, routine HPV testing is not recommended.</i> "
Participant 6	"Residual tumour. How would I know how much is left behind? It is not something that I can get from the pathology examination."
Participant 7	"So just take out the last sentence. The R status and P 16."
Participant 6	<i>"Tumour localization, macroscopic tumour size, histological tumour type, histological tumour grade, depth of invasion, pattern of invasion, lymphatic, vascular and perineural invasion, locally infiltrated structures, pT classification, details of affected areas and infiltrated structures. All this are in the minimum data set that what give you."</i>
Participant 3	"Do you want to put that marking or the orientation of the tumour inside here? I think marking is very important especially when there is a residual tumour. They have some important input on patients' survival."
Participant 6	"We only reported what you are giving us. If you feel it is important for your localization. The more you mark the more samples we have to take. To really sample that marking."
Participant 3	"The statement <i>anatomical topography must be clearly indicated</i> in the recommendation covers everything. The suture markers or colour coding were also stated there. That is quite good. That has been covered. That's the meaning of it but we remove the R status. I don't know what is R ⁺ status because that is already covered by the margin. If you do a marking nicely, the colour coded and that kind of thing, there is no issue of R status anymore"
Participant 2	"Maybe we remove the R status and put in the tumour margin. Maybe the Belgian says margin as R status. So we put as <i>exact tumour margin.</i> "

2. Treatment.

The participants had commented on some recommendations as listed below:

- a. Recommendation 2.1: Multidisciplinary involvement
- b. Recommendation 2.2: Pre-treatment assessment.
 - 2.2.1 Dental Evaluation.
- c. Recommendation 2.3: Treatment of Primary Non-metastatic Oral Cancer
 - 2.3.2 Early Stage of Oral Cancer (Stage I and Stage II)
 - 2.3.3 Advanced stage of Oral Cancer (Stage III and IV)
 - 2.3.4 Management of the neck lymph nodes
- d. Recommendation 2.4: Treatment of Very Advanced-stage of Oral Cancer
(M0) T4(b), any N or Unresectable Nodal Disease or Unfit for Surgery

a. Recommendation 2.1: Multidisciplinary Involvement

In reviewing the recommendations, a participant said that the list of multidisciplinary members was incomplete because the Maxillofacial Technologist was not in the list of non-core team members. Another participant mentioned about the double entry of the term *pathology*. They suggested the term remains as pathology which covers both Oral and General Pathology. Verbatim of the participants are displayed in Table 4.19.

Table 4.19: Participants' comments regarding the multidisciplinary involvement

Participant	Verbatim
Participant 1	"We missed the Dental Technologist because they are also part of the team."
Participant 3	"I think better put as Maxillofacial Technologist."
Participant 1	"In 2.1, the word pathology is repeated twice. Is it meant for the different type of specialists?"
Participant 2	"I don't think you need to specify either Oral or General Pathology."
Participant 7	"Both of them are important. In some centres, where the Oral Pathologist is too far, we sent to the General Pathologist to get a faster result."

b. Recommendation 2.2: Pre-treatment Assessments

A participant mentioned that the term *status* needed to be added after the word periodontal to make the statement more explicit. Verbatim of the participant is displayed in Table 4.20.

Table 4.20: Participant's comment regarding the pre-treatment assessments

Participant	Verbatim
Recommendation 2.2.1: Dental evaluation	
Participant 3	"Just a little bit of grammar correction for the statement of <i>the evaluation should include panoramic oral radiograph (OPG), risk assessment of caries and periodontal</i> . I think we need to add <i>status</i> after the periodontal."

c. Recommendation 2.3: Treatment of Primary Non-metastatic Oral Cancer

Recommendation 2.3.2: Early Stage of Oral Cancer (Stage I and Stage II)

Context: Early Stage of Oral Cancer (Stage I and Stage II)

One participant thought that the statement *Early Stage of Oral Cancer (Stage I and Stage II)* is not valid for this context if the staging is based on histopathological diagnosis. Extracapsular spread which is mentioned in recommendation 2.3.2 (j) is a pathological feature of stage IV cancer. Therefore, they suggested the statement be replaced with Clinical Staging (Stage I and II) to show that the staging is based on clinical diagnosis.

Recommendation 2.3.2 (g,h)

Few participants suggested changing the term *re-resection to re-excision* to make the wording clearer and more explicit.

Recommendation 2.3.2(i)

It was recommended that *Postoperative radiotherapy should be considered for patients with clinical and pathological features that indicate a high risk of recurrence.* The participants stated that the term *pathological feature* in the recommendation was deemed to be vague. A participant mentioned that the pathological features such as vascular invasion and extracapsular spread are not reliable indicators in considering treatment for the early stage of Oral Cancer (Stage I and Stage II) as compared to the more important factor which is the tumour margin. As the context of pathological features is not clearly explained, the recommendation was suggested to be omitted by the participants. It was emphasized by a participant that postoperative radiotherapy should be considered with care for Stage I and Stage II cases due to lifelong post radiotherapy complication.

Additional recommendation: Primary Radiotherapy

A participant mentioned that primary radiotherapy should be offered to patients who are concerned about the restoration of form and function or those who are afraid of surgery although they have to bear with the long term side effect. It is currently practiced by other participants and they thought that this information needs to be addressed in the guideline. However, in reviewing the recommendations, it was realised that this information has been covered in the recommendations 2.3.2 (e). Verbatim of the participants are displayed in Table 4.21.

Table 4.21 Participants' comments regarding the Early Stage of Oral Cancer (Stage I and Stage II)

Participant	Verbatim
Context	
Participant 2	"The statement of the early stage of oral cancer is for clinical diagnosis or pathological diagnosis? If pathological diagnosis, why you have extracapsular spread here."
Participant 7	"Extracapsular is actually a histopathological diagnosis. Aggressive tumour you know!"
Participant 3	"Why extracapsular spread here. Even extracapsular is already stage IV, cannot be stage III anymore. This statement is not valid. Why you put the statement for stage IV in Stage I and II?"
Participant 2	"It is quite contradicting. That's mean this is clinical staging and not a histopathological diagnosis."
Participant 6	"That's mean this is clinical stage I and II, based on the tumour size."
Participant 7	"It is a clinical diagnosis. The staging is based on CT scan or MRI. What do you feel clinically for lymph nodes?"
Recommendation 2.3.2 (g)	
Participant 6	"For recommendation 2.3.2(g), <i>re-resection</i> sound lousy for the recommendation. Why don't we say as repeat resection or something else?"
Participant 2	"I think this means additional resection. We just go to the area that we missed."
Participant 2	"I think <i>re-excision</i> sounds better for the recommendation (g). Also for the recommendation (h)."
Recommendation 2.3.2(i)	
Participant 3	"How about recommendation (j). What do you think? <i>What are the pathological features that indicate a high risk of recurrence?</i> Is it tumour grade? We have to consider with care for the postoperative radiotherapy. I am not sure whether it is justified or not to give radiotherapy for stage I and II because of the lifelong adverse effect."
Participant 6	"Maybe it is poorly differentiated one. It is an aggressive tumour."
Participant 7	"It is quite subjective. Maybe it is outside the extra-capsular."
Participant 3	"But this one is stage I or II."
Participant 3	"I think the pathological features in not reliable. The more reliable is the tumour margin. Even it is well differentiated or not, if the margin is dysplastic. I will treat."
Participant 6	"Unless this is the one that we say we are seeing the vascular invasion as well. That is something that you only see in pathology."
Participant 3	"There are tumours, normally does not see at stage I and II. Aggressive tumours with no diffuse margin or we cannot see the margin and not resectable at the first place."
Participant 2	"My oncologist will not shine if the margin is not clear. Even though, if we say this is young patient or aggressive tumour. It was expanding rapidly. It can cause radiation-induced tumour."

“Table 4.21 continue”

Participant	Verbatim
Participant 3	“If everyone agrees I would like to omit this statement. Moreover, we don’t practice this at this moment.”
Participant 2	“As we don’t know the context of pathological features that indicate a high risk of recurrence, I think we should remove this recommendation.”
Additional recommendation: Primary Radiotherapy	
Participant 3	“You did not put here a recommendation on Primary Radiotherapy for those healthy or normal patients. Some of them did not want to go for surgery. Good for T2/T3 you radiate it as a first choice without any loss of tissue. In term of survival, the result is not different between surgery and radiotherapy but radiotherapy has worst long-term side effects. However, it has good restoration of form and functions, for example, the lip and tongue are still intact.”
Participant 2	“Correct me if I am wrong. Can we recommend radiotherapy for patient with stage I of tongue carcinoma?”
Participant 3	“For T1, you don’t have to. You can remove. Usually, T1 does not cause any deformity in form and functions. If you radiate it, the patient will have lifelong xerostomia and other complications such as oral mucositis. You just cut and send patient home. However, if the patient refused surgery or is afraid of surgery, that is fair enough. Tell the patient that you will have lifelong radiotherapy complication. If the patient agreed to go for surgery, you should not radiate T1.”
Participant 3	“I will give you the evidence from the England Medical Journal. I think a better statement is <i>Primary radiotherapy can be considered to T2 or T3 tumour for patients who refused surgery</i> . Sometimes, it is the surgeon’s preference for not conducting surgery on T2 cases that can cause deformity, no matter you construct.”
Participant 7	“There are several patients, we do that. I have one patient who refused surgery. We radiated and she still walks around.”

Recommendation 2.3.3: Advanced Stage of Oral Cancer (Stage III and IV)

For recommendation 2.3.3 (a): *Patients with resectable disease who are fit for surgery should have surgical resection with reconstruction*, a participant suggested the term *whenever possible* is added after the word reconstruction. For recommendation 2.3.3 (i), even though neo-adjuvant chemotherapy to radiotherapy is commonly practiced by several participants, they decided to maintain the recommendation for the reason that they are not the experts in that field. Verbatim of participants are displayed in Table 4.22.

Table 4.22 Participants' comments regarding the advanced stage of Oral Cancer

Participant	Verbatim
Recommendation 2.3.3 (a)	
Participant 2	"I would like to suggest we add <i>whenever possible</i> after the word reconstruction in the recommendation 2.3.3 (a)."
Recommendation 2.3.3 (i)	
Participant 1	"For the recommendation 2.3.3 (i), sometimes this depends on the Oncologist. The neo-adjuvant chemotherapy may increase the sensitivity of the tumour to radiation. We do a lot of cases particularly for patient with a huge carcinoma in order to increase the sensitivity of the tumour to radiation."
Participant 3	"It is quite standard. Maybe the Oncologist referred to the word routine. It is supported by high level of evidence. Maybe it is meant for special cases."
Participant 2	"When we need to buy time."
Participant 7	"I have spoken to the Oncologist, to give radiotherapy to my patient with tongue carcinoma in order to shrink the tumour before we excise it. Some of them don't like it. They prefer we excise and reconstruct."
Participant 7	"They think differently based on where they were trained. To me, I will leave this as it is. This is not our expertise."
Participant 2	"Maybe they are looking for a routine. They are giving themselves some rooms."

Recommendation 2.3.4: Management of the neck lymph nodes

For the recommendation 2.3.4 (b): *Perform a selective neck dissection of at least level I, II and III in all patients with a cNOMO oral cavity SCC that is treated surgically*, participants suggested certain parameters need to be considered in performing selective neck dissection for patients with cNOMO such as *site, grade, pattern of invasion, lymphatic infiltration, and choice of reconstruction*. Verbatim of the participants are displayed in Table 4.23.

Table 4.23 Participants' comments regarding the management of the neck lymph nodes

Participant	Verbatim
Recommendation 2.3.4 (b)	
Participant 2	"In the recommendation 2.3.4 (b), we need to go for other parameters, it is not straightforward for Level I, II and III neck dissection because some area N0 neck such as maxilla, we don't do neck dissection. It is not for all patients."
Participant 7	"If it is maxilla, no, but if it is floor of the mouth, we do. That's fair. Maybe you want to qualify where."
Participant 3	"For N0, I will consider the pattern of invasion, lymphatic infiltration beside tumour size and grade for the neck dissection."
Participant 2	"Site, grade, pattern of invasion, lymphatic infiltration, and choice of reconstruction."

d. Recommendation 2.4 Treatment of Very Advanced-stage of Oral Cancer (M0)

T4(b), any N or Unresectable Nodal Disease or Unfit for Surgery

Tumour downstaging is a process of treating patients with chemoradiotherapy in order to enable surgery. Even though the evidence is limited, it is commonly practiced by the participants because a lot of their patients presented at late stage. Therefore, the related recommendation was added in the guideline based on the participants' experience. Verbatim of the participants is displayed are Table 4.24.

Table 4.24 Participants' comments regarding the Treatment of Very Advanced-stage of Oral Cancer

Participant	Verbatim
Participant 3	"For T4(b) Oral cancer, I downstage the tumours by giving chemotherapy until they came into a region where we can resect it. It is not mentioned here. <i>Chemoradiotherapy should be considered to downstage the tumour.</i> A lot of our patients present at late stage."
Participant 1	"Yes, in Sabah we have to downstage many patients."
Participant 7	"In Hospital Kuala Lumpur, we are also doing the same thing."
Participant 3	"The evidence is limited."

3) Follow-up care

Participants had commented on some recommendations for follow-up care as listed below:

- a. Recommendation 3.1: Clinical and Imaging Evaluation
- b. Recommendation 3.2: Dental Rehabilitation
- c. Recommendation 3.5: Psychosocial Support

a. Recommendation 3.1: Clinical and Imaging Evaluation

It was recommended in the guideline that *follow-up frequency, even in symptom-free individuals, should be at least every 3 months in the first and second year, every 6 months in the third to fifth year, and annually afterward*. However, based on the characteristics of local patients, the participants preferred the follow-up frequency for every case to be monthly for the first 2 years, 3 monthly for the next 3 years and 6 monthly after 5 years. Verbatim of the participants are displayed in Table 4.25.

Table 4.25 Participants' feedback regarding the clinical and imaging evaluation in follow-up care

Participant	Verbatim
Participant 3	"It depends on the risk of the patient. For high risk patients, I will review patients monthly for the first 2 years, 3 months for the third year."
Participant 2	"Most of our patients are high risk. Commonly, they present at late stage. We prefer patients to be reviewed monthly for the first year. We are worried about the residual tumour. What we have been taught was monthly for the first 2 years, 3 monthly for the next 3 years and 6 monthly after 5 years."
Participant 4	"Do you follow-up those patients who default?"
Participant 3	"We called patients as much as we could. Just to find the status of the patients. We are not bad in term of follow-up. Most of the turned up, even though not 100%."

b. Recommendation 3.2: Dental rehabilitation

Recommendation 3.2 (a)

The recommendation states that *surgical interventions (e.g. extractions) should be performed by professionals with experience in treating patients with head and neck cancer*. The participants had a different opinion regarding who should perform the surgical procedure during postoperative care. A few participants thought that the procedure should be carried out by the dental professional at the hospital set-up. Meanwhile other participants stated that some of their patients needed to be reviewed at the sub-centres particularly for patients who live far away from the hospital. After considering both situations, finally it was agreed upon by all participants that the recommendation was fair and acceptable and is to be maintained.

Recommendation 3.2 (b)

A participant mentioned that the term *infected* in recommendation 3.2 (b) *Infected osteoradionecrosis of the jaw is a serious treatment complication that should be managed in specialized centres* should be removed because Osteoradionecrosis itself means ‘dead bone with super infection’. Subsequently, the term *specialized centres* was re-spelt as *specialised centres* in response to one participant’s comment. Verbatim of the participants are displayed in Table 4.26.

Table 4.26 Participants’ feedback regarding the dental rehabilitation

Participant	Verbatim
Recommendation 3.2 (a)	
Participant 3	“In the recommendation 3.2 (a), regarding the dental rehabilitation. Does that mean, the surgical intervention should be performed by the Dental Officer at the hospital set up?”
Participant 4	“I would agree if you specifying the hospital. We at the primary care are not really sure of the management.”

“Table 4.26 continued”

Participant	Verbatim
Recommendation 3.2 (a) continue	
Participant 3	“Moreover the facility for community level or sub-centre is very limited. You can’t identify osteonecrosis.”
Participant 7	“We reviewed patients during our traveling to the sub-centre or dental clinic. Sometimes, patients are seen by the trained professional including the extraction.”
Participant 6	“In the existing guideline for early detection of pre-cancerous and oral cancer, the patients will be referred back to the primary care after surgery for follow-up care. In the primary care, they are not doing much on surgical intervention, if they find anything suspicious, they will send back patients to the tertiary care.”
Participant 1	“In Sabah, we have a team. For example, those patients from Kota Belud which is about 200 km away, we did surgery at the Kota Kinabalu. We liaised with the main dental clinic at Kota Belud for follow-up care. We will go there at least once a month and reviewed the patients. “
Recommendation 3.2 (b)	
Participant 1	“3.2 (b) Infected osteoradionecrosis. Osteoradionecrosis then infected some more.”
Participant 3	“Yes, osteonecrosis is defined as dead bone with super infection. How about the term specialized centres? We should follow British or American?”
Participant 6	“When we write it, then this will become our document. It should be British.”

c. Recommendation 3.5: Psychosocial Support

In response to the recommendation that *patients with oral cavity cancer (and their family, carers) should be offered dedicated psychosocial support on a continuous basis within the context of a multidisciplinary team*, the participants stressed the importance of psychosocial support for the patients in order to optimise their quality of life. A participant thought that the Clinical Psychiatrist should be included as the core member of multidisciplinary team to ensure their commitment in managing oral cancer patients. However, certain indicators need to be considered in patient referral such as behavioural

change, denial or poor adjustment so as not to overburden the Psychiatrists. Participants' verbatim are displayed in Table 4.27.

Table 4.27 Participants' feedback regarding the psychosocial support

Participant	Verbatim
Participant 3	"In university, our Psychiatrists could not bear the workload. Every day there were full of patients. We referred patients to the social worker. We have psychologists at the Social Worker Department."
Participant 1	"In Sabah, we have speech therapists but swallowing rehabilitation, that one ENT will take care. Psychosocial support we also have."
Participant 7	"In postradiotherapy and post-surgery. When patients tell you that he wants to commit suicide, you must quickly refer to Psychiatrists. That 's one thing that sometimes we missed."
Participant 2	"Once vocalised, we need to refer the patients to the Psychiatrist."
Participant 3	"We will refer patients for some reasons such as behavioural changes, no eye focus etc. If we recommended as routinely, I am worried, the Psychiatrist won't be able to bear the workload."
Participant 1	"In that sense, I think the Clinical Psychiatrist has to be in the core team. They are not listed in the core team. "

4.4.3.2 Summary of the Evidence

This section illustrated the details summary of evidence used to develop the recommendations. Participants commented on several parts and minor modifications were made based on their feedback. These related parts are documented below:

a. Imaging of neck lumps and nodes

This section explained the accuracy of certain procedures such as CT scan, MRI, USNFA and FGD-PET in detecting neck nodes metastases. Few participants thought that the evidence presented by Julia Woolgar, (1994) about the incidence of 27% false negative for the clinically negative neck (based on clinical examination and CT imaging) needs to be added to the discussion. This is to inform surgeons that CT imaging is not an accurate procedure in detecting neck nodes. It has to be confirmed

with histological assessment as well. The evidence was added to the segment. Participants' verbatim are displayed in Table 4.28.

Table 4.28 Participants' feedback regarding the evidence imaging of neck nodes

Participant	Verbatim
Participant 3	"I suppose that, it is important to put a paper by Julia Woolgar. She reported about chances of 27% of false negative for CT scan. It means that you cannot detect the node during the CT scan when histopathological assessment showed 27% positive nodes. I have the paper. It is very important because CT scan is not the imaging to detect the neck nodes. We have to consider micrometastasis as well. We want to put in surgeons mind that it is not the procedure to the detect neck nodes."
Participant 6	"Although you have done the imaging, it does not mean that negative node is a negative neck."

b. Dental Evaluation

As this segment discusses both the oral and dental management, participants said that the statement should be coded as oral and dental evaluation instead of dental evaluation alone. Participants' verbatim are displayed in Table 4.29.

Table 4.29 Participants' feedback regarding the evidence for dental evaluation

Participant	Verbatim
Participant 1	"If you refer to the section on page 29, this part you also mention both dental and oral management. That's mean there are both soft tissue and hard tissue components there. If you put only dental evaluation, to me it is a bit misleading."
Participant 6	"Dental, basically means more toward teeth. You look at the tongue, cheek, lip, you know, buccal mucosa and retromolar area. All that's oral already, apart from teeth."

c. Surgery

The participants thought that the statement *in considering reconstruction, it must be considered that a distance of less than 1 mm between the histologically demonstrated*

tumour margin and the resection line counts as a positive margin of resection needed clarification. They mentioned that the word *in considering reconstruction*, is not relevant to the rest of the statement. Contrary to what is stated, reconstruction is carried out immediately and cannot be considered based on histologically tumour margin. After an extensive discussion, the participants agreed that the word *in considering reconstruction* is modified to *for optimum tumour control* because they thought that the statement is suitable to explain about the tumour control rather than reconstruction. Participants' verbatim are displayed in Table 4.30.

Table 4.30 Participants' feedback regarding the evidence for surgery

Participant	Verbatim
Participant 3	" <i>In considering reconstruction, it must be considered that a distance of less than 1 mm between the histologically demonstrated tumour margin and the resection line counts as a positive margin of resection.</i> I want to know the meaning of this sentence. Thus it meant that if the margin is not clear then you are not considering reconstruction."
Participant 3	"You cannot consider reconstruction based on margin. The margin will only be achieved later on. The reconstruction will be carried out immediately unless secondary reconstruction is needed later on."
Participant 1	"The word <i>in considering</i> , means when you cut, you can't immediate do reconstruction, you have to wait for the HPE result. By right, we reconstruct immediately."
Participant 3	"Probably this has more inference on the success of the surgery itself rather than for reconstruction. I mean the ability to control the disease rather than to consider a reconstruction."
Participant 3	"We omit the word reconstruction and replace it with <i>for optimum tumour control.</i> "
Participant 7	"I have read a lot of German Journals. It took me sometime to understand the meanings in the journal. Maybe because of the way they translate it in English, therefore it has that meaning. Like what Panel 3 said, after you pick the tissue out, whether the margin is clear or not, we will reconstruct, later on we will see whether the margin is achieved or not."
Participant 2	"Did the word come from the journal?"
Participant 3	"But you can critically comment on his because this one doesn't have the flow of the current practice."
Participant 7	"Maybe he meant for frozen section."
Participant 3	"If frozen section, also I would not agree. For frozen section, it is yes or no, clear or not clear. We cannot say in mm. Formalin section, yes, it is mm."

d. Dental Rehabilitation

As this segment discusses both the oral and dental management, a participant said that it should be coded as *Oral rehabilitation* instead of *Dental Rehabilitation*. The verbatim of the participant is displayed in Table 4.31.

Table 4.31 Participant's comment on evidence for dental rehabilitation

Participant	Verbatim
Participant 1	"If you put Dental rehabilitation per se, that can be misleading. If you say dental caries, periodontal disease, that is alright. But you mentioned involvement of Osteoradionecrosis, I think instead of putting dental rehabilitation, we need to change it to oral rehabilitation, so we cover everything. The word of dental, we change to oral."

4.4.4 Algorithm for Management of Oral Cancer

This segment illustrated the flow of the process to be followed in managing oral cancer patients. Generally, the participants found that all relevant information were already included in the algorithm except that some modifications that are needed to make it more complete. A few comments on the algorithm were received from the participants including to add on 'patients expectation' in the pre-treatment, 'quality of life' should be assessed during pre-treatment and post-treatment phases, 'the management of the lymph nodes' should be placed in between the treatment and post-treatment procedure, and finally the 'tumour downstaging procedure' and 'criteria to perform a selective neck dissection' need to be updated in the algorithm. In the final version of the guideline (see Appendix Q), the algorithm is modified based on the participants' comments. Verbatim of the participant are displayed in Table 4.32

Table 4.32 Participants' comments regarding the algorithm for management of oral cancer

Participant	Verbatim
Participant 1	"For the pre-treatment assessment, would it ok if we add in patients expectation here."
Participant 6	"I think put under pre and post-treatment assessment, the quality of life assessment."
Participant 1	"When we are talking about assessment, we have to set a standard of questionnaire to be used in all centres."
Participant 1	"The management of the lymph nodes should be before the post-treatment. You have to move the boxes in between the treatment and post-treatment."
Participant 3	"Where are you going to put the tumour downstaging recommendation and criteria to perform a selective neck dissection in the algorithm?"

4.4.5 Clinical Audit Indicator

The participants were asked about clinical audit indicators to be used for quantifying the quality improvement or expected outcome after implementing this guideline. A participant suggested two potential indicators including 1) monitoring the follow-up protocol; 2) the treatment time from surgery to completion of radiotherapy. Verbatim of the participants are displayed in Table 4.33

Table 4.33 Participant comment regarding the clinical audit indicator

Participant	Verbatim
Participant 2	"One thing is how well we follow-up the cases. Let say we have protocol of one month. How well we keep with this".
Participant 2	"I think this can be the other indicator. The treatment time from surgery to completion of radiotherapy."

4.4.6 The Concerns of the Specialists

The participants' comments that are not directly related to the objective of the FGD are discussed below. Firstly, they expressed their concerns about patient delay. A lot of

oral cancer patients presented themselves at the late stage. Based on the participants' experience, the most important contributing factor for patient delay was the patients' preference to seek for alternative therapy rather than seeking professional help. Moreover, media plays an important role in advertising alternative products and has gained a lot of people's confidence that such products can cure cancers. Only at late stage, the patients came to see health professionals whereby more invasive and destructive treatment procedures were required which was associated with poor prognosis. This is an issue which health care providers should place great emphasis on educating patients; about the importance of seeking professional help as soon as oral symptoms develop. The participants' verbatim are displayed in Table 4.34.

Table 4.34 Participant's comment on patient delay

Participant	Verbatim
Participant 4	"We have cases diagnosed as cancer, but they did not turn up for the treatment."
Participant 3	"I dispute the media for advertising the alternative products. They create confidence among the people and we have a lot of problems with it. My colleagues also shared this. In advertisements, when they claimed that their products cure to cancer, they need to be careful."
Participant 3	"From my observation, when all my patients go for alternative therapy, all my patients died. They came back at late stage. Cannot cure. I have one patient. She came to me at T1, I removed a bit. After that she went for alternative therapy. When she came back, I have to remove the whole maxilla. I invited her to speak to the public about the alternative therapy."
Participant 1	"When they came to us at late stage, they demanded so much from us. "I want my face to be like this", "I want my tongue to be able to move around". After all the explanations, they still came and asked for that."

As majority of the recommendations were accepted without modification, a participant expressed his concern about plagiarism issue in thesis and suggested rephrasing the recommendations based on their understanding. It was emphasized to the participants that, in the earlier process, a multidisciplinary group of expert panels had done the initial filtering and decided to accept the 81 recommendation as it is.

Therefore, the interpreting of the Turnitin has to be treated differently because this is part of standard methodology used in developing the guideline. Verbatim are displayed in Table 4.35.

Table 4.35 Participant's comment on plagiarism

Participant	Verbatim
Participant 2	"We have been informed that out of 91 recommendations, 81 were accepted without modification, 10 were modified."
Participant 3	"Is it allowed or not that the 81 recommendations that were fully adopted will be accepted when we enter in the Turnitin? I am worried it will be cause the allowance of 20% plagiarism to be exceeded. I am concerned about that."
Participant 3	"Is it possible that we modify the sentences? I mean for analytical interpretation. The statement will be based on our understanding so that it would not be captured in the Turnitin."
Participant 2	"This guideline comes from other guidelines, which I assumed to come from another guideline. Whatever guideline was produced is an amalgamation of recommendations of other guidelines and we are further amalgamating it. Do we still have the same weight for plagiarising the other guidelines"?"

4.5 Finalising Best Practice Guidelines for Oral Cancer Management in Malaysia

4.5.1 The Second Version of Draft Guidelines

In response to the participants' comments during the FGD, minor changes were made on several segments of the first version of the draft guideline (Table 4.36, 4.37 and 4.38). The changes made were highlighted in red in the tables. However, the format of the guideline remained as participants found this section to be clear and well organised.

The modifications made to the draft guideline are presented in three parts including:

4.5.1.1 Section I (Introduction) and Section 2 (Development of the Guideline)

4.5.1.2 Section 3 (Clinical Recommendations) and Summary of the Evidence

4.5.1.3 Algorithm for Management of Oral Cancer

4.5.1.1 Section I (Introduction) and Section 2 (Development of the Guideline)

Table 4.36: Modification made on Section I (Introduction) and Section 2 (Development of the Guideline)

Segment	Original Statement in the Draft Guideline	Modified Statement in the Draft Guideline
1.4	<p>Target Users</p> <p>The guideline is applicable to all healthcare professionals managing oral cancer patients including oral and maxillofacial surgeons, head and neck surgeons, oral pathologists, clinical oncologists, radiologists, plastic and reconstructive surgeons, dentist, nurses, speech and swallowing therapists, nutritionists and psychosocial workers.</p>	<p>Target Users</p> <p>The guideline is applicable to all healthcare professionals managing oral cancer patients including Oral and Maxillofacial Surgeons, General Head and Neck Surgeons, Otorhinolaryngologist (ENT), Oral Pathologists, Clinical Oncologists, Radiologists, Plastic and Reconstructive Surgeons, Dentists, Nurses, Speech and Swallowing Therapists, Nutritionists and Psychosocial Workers.</p>
2.6	Not available	<p>The proposed clinical audit indicators for quality management are:</p> <p>a) Proportion of patients turned up for follow-up care.</p> <p>b) Proportion of patients completed radiotherapy within 14 weeks after surgery (in the absence of postoperative medical or surgical complications).</p>

4.5.1.2 Section 3 (Clinical Recommendations) and Summary of the Evidence

a) Clinical Recommendations

Table 4.37: Modification made on Section 3 (Clinical Recommendations)

Segment	Original Recommendation in the draft	Modified Recommendation
1) DIAGNOSIS		
Recommendation 1.3: Biopsy		
1.3 (a)	A biopsy should be taken from the most suspect part of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.	A biopsy should be taken from the most suspected part(s) of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.
1.3 (b)	When a patient with a diagnosis of oral squamous cell carcinoma is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical squamous cell carcinoma should be reviewed by an expert from a reference laboratory.	When a patient with a diagnosis of oral squamous cell carcinoma is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical squamous cell carcinoma should be reviewed by an expert from a reference laboratory.
Recommendation 1.5: Imaging of locally advanced stage tumour		
1.5 (a)	In patients presenting with cervical lymph node metastases, where CT or MRI does not demonstrate an obvious primary tumour, Fluorodeoxyglucose positron emission tomography - computed tomography (FDG-PET) should be performed as the next investigation of choice.	In patients presenting with cervical lymph node metastases, where CT or MRI does not demonstrate an obvious primary tumour, Fluorodeoxyglucose positron emission tomography - computed tomography (FDG-PET) should be performed as the next investigation of choice, whenever possible .

“Table 4.37 continued”

Segment	Original Recommendation in the Draft	Modified Recommendation
1.5 (b)	In patients presenting with suspected recurrent head and neck cancer, where CT/MRI does not demonstrate a clear cut recurrence, FDG-PET should be performed as the next investigation of choice.	In patients presenting with suspected recurrent head and neck cancer, where CT/MRI does not demonstrate a clear cut recurrence, FDG-PET should be performed as the next investigation of choice, whenever possible .
1.9.2 Histopathology reporting		
1.9.2	<p>For discussion with the clinician, the histopathological findings must describe the exact localization of any existing R+ status. The anatomical topography must be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding. The histopathological result must include:</p> <ul style="list-style-type: none"> • tumour localization, • macroscopic tumour size, • histological tumour type, • histological tumour grade, • depth of invasion, • pattern of invasion, • lymphatic, • vascular and perineural invasion, • locally infiltrated structures, • pT classification, • details of affected areas and infiltrated structures, • R status and p16 (if not done on biopsy). 	<p>For discussion with the clinician, the histopathological findings must describe the exact tumour margin. The anatomical topography must be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding. The histopathological result must include:</p> <ul style="list-style-type: none"> • tumour localization, • macroscopic tumour size, • histological tumour type, • histological tumour grade, • depth of invasion, • pattern of invasion, • lymphatic, • vascular and perineural invasion, • locally infiltrated structures, • pT classification, • details of affected areas and infiltrated structures

“Table 4.37 continued”

Segment	Original Recommendation in the Draft	Modified Recommendation
2) TREATMENT		
2.1 Multidisciplinary involvement		
	<p>a. Treatment plans should be formulated by a multidisciplinary team (core members and non-core member) in consultation with the patients and family member caregiver.</p> <p>The core members comprise the specialist disciplines of:</p> <ul style="list-style-type: none"> • Oral and Maxillofacial Surgery, • Otorhinolaryngology, • Pathology, • Clinical Oncology, • Pathology • Radiology, • Plastic and Reconstructive Surgery. <p>The non-core members comprise of:</p> <ul style="list-style-type: none"> • General Practitioner, • Dentist, • Nursing Care, • Speech and Swallowing Therapist, • Nutritional Therapist, • Psychosocial Worker. 	<p>a. Treatment plans should be formulated by a multidisciplinary team (core members and non-core member) in consultation with the patients and family member or caregiver.</p> <p>The core members comprise the specialist disciplines of:</p> <ul style="list-style-type: none"> • Oral and Maxillofacial Surgery, • Otorhinolaryngology, • Pathology, • Clinical Oncology, • Radiology, • Plastic and Reconstructive Surgery. • Clinical Psychology. <p>The non-core members comprise of:</p> <ul style="list-style-type: none"> • General Practitioner, • Dentist, • Nursing Care, • Speech and Swallowing Therapist, • Nutritional Therapist, • Psychosocial Worker, • Maxillofacial Technologist.
2.2 Pre-treatment Assessment		
2.2.1	<p>Patients with head and neck cancer, especially those planned for resection of oral cancers or whose teeth are to be included in a radiotherapy field, should have the opportunity for a dental or prosthodontics evaluation by an appropriately experienced dental practitioner. The evaluation should include panoramic oral radiograph (OPG), risk assessment of caries and periodontal. The dental practitioner should give preventive advice and perform necessary restorative or prosthodontic work.</p>	<p>Patients with head and neck cancer, especially those planned for resection of oral cancers or whose teeth are to be included in a radiotherapy field, should have the opportunity for a dental or prosthodontics evaluation by an appropriately experienced dental practitioner. The evaluation should include panoramic oral radiograph (OPG), risk assessment of caries and periodontal status. The dental practitioner should give preventive advice and perform necessary restorative or prosthodontic work.</p>

Table 4.37 continued”

Segment	Original Recommendation in the Draft	Modified Recommendation
2.3 Treatment of Primary non-metastatic Oral Cancer		
2.3.2 Clinical Staging (Stage I and II)	<p>g. Re-resection should be considered to achieve clear histological margins if the initial resection has positive surgical margins or if inadequate initial excision biopsy has been performed.</p> <p>h. Re-resection is not possible, postoperative radiotherapy should be considered.</p>	<p>h. Re-excision should be considered to achieve clear histological margins if the initial resection has positive surgical margins or if inadequate initial excision biopsy has been performed.</p> <p>i. If re-excision is not possible, postoperative radiotherapy should be considered</p>
2.3.3 Clinical Staging (Stage III and IV)	a. Patients with resectable disease who are fit for surgery should have surgical resection with reconstruction.	a. Patients with resectable disease who are fit for surgery should have surgical resection with reconstruction, whenever possible.
2.3.4	b. Perform a selective neck dissection of at least level I, II and III in all patients with a cNOM0 oral cavity SCC that is treated surgically.	b. Perform a selective neck dissection of at least level I, II and III in all patients with a cNOM0 oral cavity SCC that is treated surgically, depending on site, size, grade, pattern of invasion, lymphatic infiltration and choice of reconstruction.
2.4 Treatment of very advanced-stage oral cancer (M0) T4b, any N or unresectable nodal disease or unfit for surgery.		
	Additional recommendation.	g. Chemoradiotherapy can be considered for tumour downstaging in order to enable resection.
3) FOLLOW-UP CARE		
3.1	An individually structured follow-up schedule should be devised for each patient. The quality of life, side effects of treatment, nutritional status, speech, dental status, thyroid function, smoking and alcohol consumption, etc. should be surveyed periodically. There is no evidence to support routine use of imaging techniques for the detection of locoregional or metastatic recurrence during follow-up. Follow-up frequency, even in symptom-free individuals, should be at least every 3 months in the first and second year, every 6 months in the third to fifth year, and annually afterwards.	An individually structured follow-up schedule should be devised for each patient. The quality of life, side effects of treatment, nutritional status, speech, dental status, thyroid function, smoking and alcohol consumption, etc. should be surveyed periodically. There is no evidence to support routine use of imaging techniques for the detection of locoregional or metastatic recurrence during follow-up. Follow-up frequency, even in symptom-free individuals, should be at least every month in the first and second year, every 3 months in the third to fifth year, and six monthly henceforth.

Table 4.37 continued”

Segment	Original Recommendation in the Draft	Modified Recommendation
3.2 (b)	Infected Osteoradionecrosis of the jaw is a serious treatment complication that should be managed in specialised centres.	Osteoradionecrosis of the jaw is a serious treatment complication that should be managed in specialised centres.

b) Summary of the Evidence

Table 4.38: Modification made on the summary of the evidence

Segment	Original Statement in the Draft	Modified Statement
3.2.1.1	<u>Clinical and histopathology assessments.</u> To avoid the need for repeating the biopsy, it should be representative of the most suspect part of the tumour.	<u>Clinical and histopathology assessments.</u> To avoid the need for repeating the biopsy, it should be representative of the most suspected part(s) of the tumour.
3.2.1.3	<u>Imaging of neck lumps and nodes.</u> Assessment using CT and MRI are similarly accurate in detecting neck node metastases, and are superior to physical examination (Van den Brekel et al., 1993). CT is marginally more accurate in detecting infrahyoid node metastasis. However, MRI is more accurate than CT in detecting perivisceral nodal involvement (Wilson, 1998).	<u>Imaging of neck lumps and nodes.</u> Assessment using CT and MRI are similarly accurate in detecting neck node metastases, and are superior to physical examination (Van den Brekel et al., 1993). However, CT scanning cannot be expected to achieve 100% accuracy. Woolgar et al. (1994), in their study reported that, detailed histopathological assessment showed the incidence of 27% false negative for the clinically negative neck (based on clinical examination and CT imaging). Extranodal spread of metastatic carcinoma was present in 16% of clinically negative necks. CT is marginally more accurate in detecting infrahyoid node metastasis. However, MRI is more accurate than CT in detecting perivisceral nodal involvement (Wilson, 1998).
3.2.2.1	Dental Evaluation	Oral and dental evaluation
3.2.2.3	<u>Surgery</u> In considering reconstruction, it must be considered that a distance of less than 1 mm between the histologically demonstrated tumour margin and the resection line counts as a positive margin of resection	<u>Surgery</u> For optimum tumour control, it must be considered that a distance of less than 1 mm between the histologically demonstrated tumour margin and the resection line counts as a positive margin of resection.
3.2.3.2	Dental Rehabilitation	Oral rehabilitation.

4.5.1.3 Algorithm for Management of Oral Cancer

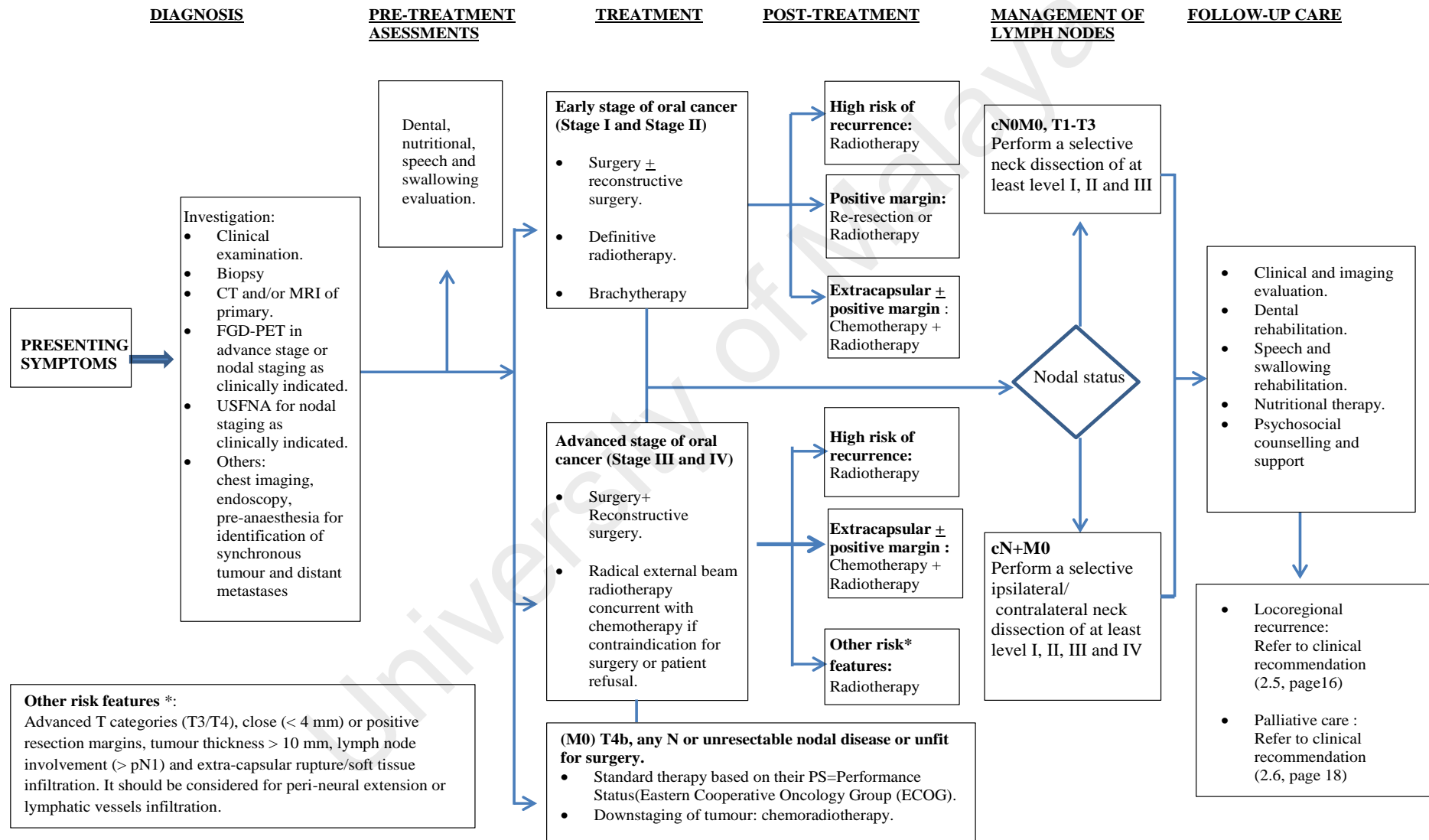


Figure 4.3 Algorithm for management of oral cancer in the first version of draft guideline

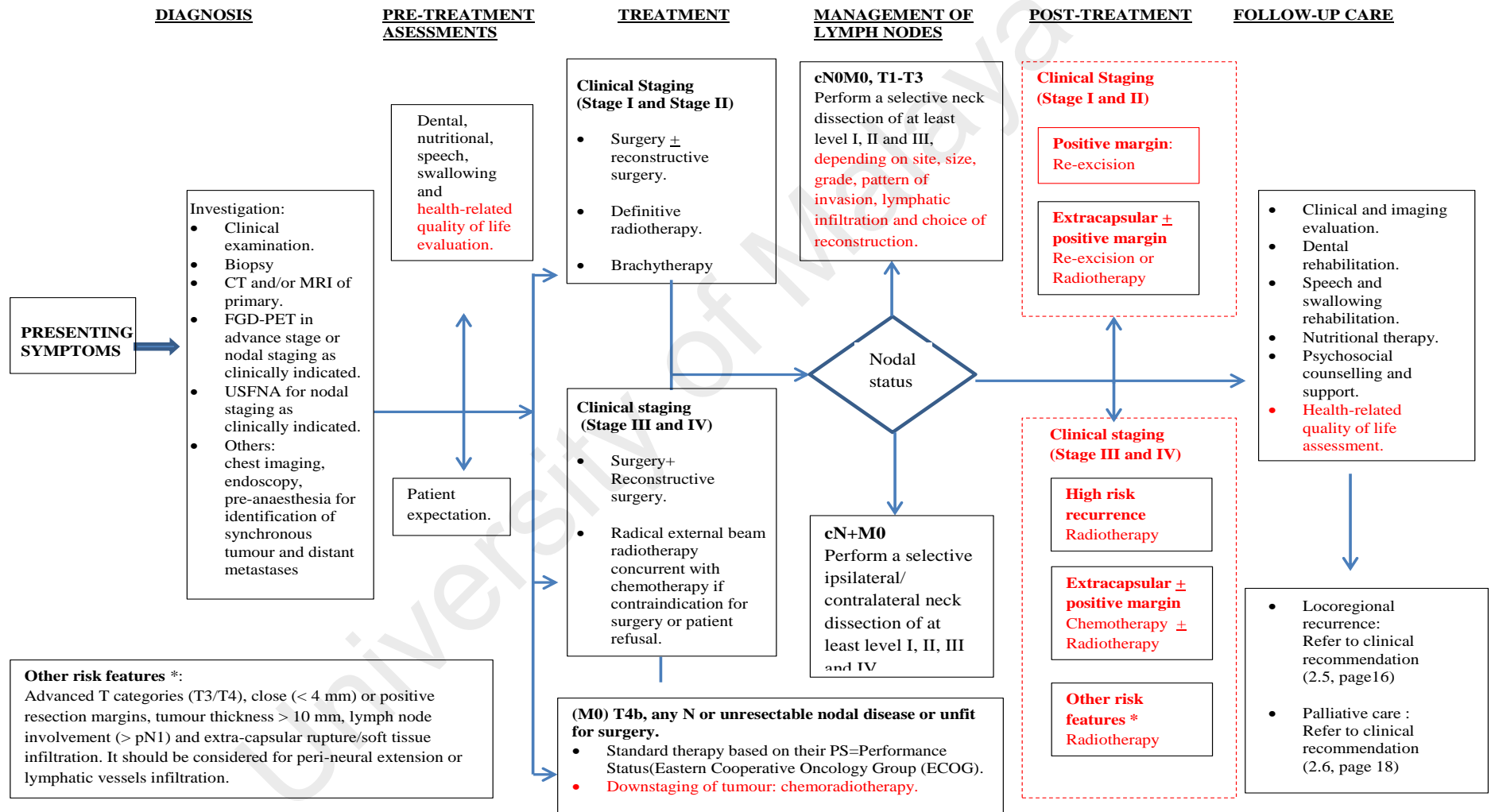


Figure 4.4 Algorithm for management of oral cancer in the second version of draft guideline

4.5.2 Final Best Practice Guideline for Oral Cancer Management in Malaysia

The second version of draft guideline was sent to all specialists through email to obtain their feedback regarding the document. Two specialists responded to the email and agreed with all the changes. Three specialists accepted the modifications with some comments as presented in Table 4.39. Two specialists did not give any feedback. The two specialists were reminded again through phone call, however, no feedback were received from them. The final version of the best practice guideline (Appendix Q) was formatted based on the comments and consensus achieved by these multidisciplinary specialists.

Table 4.39: The modifications made to the second version of draft guideline

Segment	Statement in the Second Version of Draft Guideline	Comments	Modified Statement in the Final Guideline
Section 1: Introduction			
1.4	<p><u>Target Users</u></p> <p>The guideline is applicable to all healthcare professionals managing oral cancer patients including Oral and Maxillofacial Surgeons, General Head and Neck Surgeons, Otorhinolaryngologist (ENT), Oral Pathologists, Clinical Oncologists, Radiologists, Plastic and Reconstructive Surgeons, Dentists, Nurses, Speech and Swallowing Therapists, Nutritionists and Psychosocial Workers.</p>	<p>To replace the General Head and Neck Surgeons with General Surgeons.</p>	<p><u>Target Users</u></p> <p>The guideline is applicable to all healthcare professionals managing oral cancer patients including Oral and Maxillofacial Surgeons, General Surgeons, Otorhinolaryngologist (ENT), Oral Pathologists, Clinical Oncologists, Radiologists, Plastic and Reconstructive Surgeons, Dentists, Nurses, Speech and Swallowing Therapists, Nutritionists and Psychosocial Workers.</p>

“Table 4.39 continued”

Segment	Statement in the Second Version of Draft Guideline	Comments	Modified Statement in the Final Guideline
Section 3: Clinical Recommendation (Diagnosis)			
1.3 Biopsy			
1.3 (a)	A biopsy should be taken from the most suspected part of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.	To replace the words suspected part to suspicious parts (s)	A biopsy should be taken from the most suspicious part(s) of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.
1.3 (b)	When a patient with a diagnosis of oral squamous cell carcinoma is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical squamous cell carcinoma should be reviewed by an expert from a reference laboratory	To replace the word slices to slides	When a patient with a diagnosis of oral squamous cell carcinoma is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slides and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical squamous cell carcinoma should be reviewed by an expert from a reference laboratory
Summary of the Evidence (3.2.1.1: Clinical and Histopathology Assessments)			
3.2.1.1	To avoid the need for repeating the biopsy, it should be representative of the most suspected part(s) of the tumour	To replace suspected part(s) to more suitable word suspicious part (s)	To avoid the need for repeating the biopsy, it should be representative of the most suspicious part(s) of the tumour

CHAPTER 5: DISCUSSION

The discussion is divided into five sections as follows:

5.1 Introduction

5.2 The literature search in identifying existing guidelines for adaptation.

5.3 The assessment of guidelines in terms of:

5.3.1) Quality

5.3.2) Currency

5.3.3) Clinical Content

5.4 Decision on whether to adopt or adapt guidelines for local use.

5.5 The multidisciplinary specialists' feedbacks regarding the draft guidelines for oral cancer management in Malaysia.

5.6 Finalising the best practice guideline.

5.1 Introduction

In order to enhance the quality of care, healthcare professional should be provided with tools that guide their decisions for each case. Literatures have shown the potential of practice guidelines in improving both the quality of care and patients health outcomes (Grimshaw & Hutchinson, 1995; Patkar et al., 2006; Lugtenberg et al., 2009). In this study, a comprehensive best practice guideline (CPG) detailing the best evidence-based approach for oral cancer management including the diagnosis, treatment, and follow-up care was developed for use by healthcare professionals managing oral cancer patients in the Malaysia.

In developing the guideline, the "Guideline Adaptation" concept was used as an alternative to the "De Novo Development" in order to take advantage of similar

guidelines that are already in existence. To date, there is no evidence suggesting that the concept of “Guideline Adaptation” is more superior to the “De Novo Concept” in term of the efficiency of guideline production (Fervers et al., 2006; Harrison et al., 2013). However, the guideline development using “Adaptation Concept” provides opportunities for research collaboration by sharing resources including the source of evidence, thus avoiding the full effort of starting from scratch in developing more consistent recommendation for oral cancer care (Fervers et al., 2011).

The core methodologies used in this study were the reviewing of high quality evidence and adaptation of recommendations from the existing guidelines, blended with expert judgements from a multidisciplinary group. The methodology was based on the Practice Guidelines Evaluation and Adaptation Cycle (PGEAC) by Graham et al., (2003) because the framework is designed to be more flexible and feasible in developing guideline within limited time and resources in comparison to a more complex process presented by The ADAPTE framework (The Adapte Collaboration, 2009). Using the 24 steps ADAPTE framework in adaptation of guidelines may require a high level of skill in both methodology and clinical content of the selected clinical area (Harrison et al., 2013; Chakraborty et al., 2014). As such, the 47 pages guideline was developed by following a systematic and structured process of the PGEAC as discussed in detailed in the following sections.

5.2 The Literature Search in Identifying Existing Guidelines for Adaptation

The inclusion of many data sources and use of various word combinations in the literature review had led to a large number of articles being identified. To ensure enough coverage of literatures, the search targeted a wide range of guideline publication

(form 2000 to 2016). Consequently, 3192 relevant articles were identified from various databases and websites.

The finding was relatively higher when compared to the guidelines search related to head and neck cancers that was carried out by the Scottish Intercollegiate Guideline Network (SIGN) (Scottish Intercollegiate Guideline Network, 2006) and Belgian Health Care Knowledge Centre (BKCE) (Belgian Health Care Knowledge Centre, 2014b) guideline development groups. The identified articles were 733 and 245 for the SIGN and BKCE respectively. The discrepancy between the findings may be explained by the difference of time period chosen for the literature search by SIGN (1998-2003) and BKCE (publication after 2010), and less databases covered by both guidelines. The SIGN conducted literature search on several guideline databases, Medline, Embase and CINAHL while the BKCE included MEDLINE, National Guideline Clearinghouse and Guideline International Network in the search strategy.

The identified articles were screened in two stages including the “title and abstract screening” and “full text review” in order to select the most relevant guideline for adaptation. The application of inclusion and exclusion criteria in the screening process resulted in the exclusion of a large number of irrelevant articles from the initial search result. Most of the articles were excluded because they could not be considered as guidelines (2745). Besides this, some guidelines were excluded either because they focussed entirely on a specific procedure (n=235) or their scope of were beyond the clinical area of interest (n=73). The screening process was done systematically by the researcher to ensure no articles were eliminated prematurely which may introduced a selection bias (Higgins & Green, 2008). For the full text review of the 33 remaining articles, a more restrictive procedure was used of which the decision on which articles

to include or exclude was made by the research committee to minimise the risk of bias in selecting the relevant guideline for adaptation. In consequences, 15 potential guidelines that covered all aspects of oral cancer management including diagnosis, treatment and follow-up care were selected from the total citations.

5.3 The Assessment of Guidelines

5.3.1 Quality

This study assessed the quality of existing guidelines on oral cancer management using a validated and widely used appraisal tool, the AGREE II instrument (The AGREE Next Steps Consortium, 2009). It was generally known that the AGREE II instrument provides a framework for assessment of the methodology quality and how well the guidelines development process is reported. The guideline authors were contacted to obtain relevant documents that had not been included in the full-text guidelines or not available from the corresponding guideline developers' websites to ensure most information on methods of development are available for the assessment.

Given the estimated time and work burden of the appraisal process, the fifteen selected guidelines were initially screened using the Domain Rigour of Development. The 'Rigour of Development' was used in the screening process because this domain is considered a stronger indicator for guideline quality than the other domains. The eight items comprising this domain measure the degree to which the guideline development process was evidence-based (Graham & Harrison, 2005; The AGREE Next Steps Consortium, 2009; Alonso-Coello et al., 2010).

This screening process was helpful in filtering the number of guidelines by removing those that clearly do not meet the predetermined quality score for further assessment in

the complete AGREE II appraisal. Consequently, seven guidelines were excluded based on their low performance in this domain (Scotia, 2007; Gregoire et al., 2010; Roland & Paleri, 2011; Mesía et al., 2013; South Australia Cancer Service, 2013; Fagan et al., 2014; Saskatchewan Cancer Agency, 2015). The main flaws presented by most of the excluded guidelines were lack of a systematic method in searching and selecting evidence including the method used to translate evidence into the recommendations.

The results of the complete AGREE II appraisal on eight shortlisted guidelines showed that the mean quality scores across the six domains were moderate, ranging from 48.9% to 83.1%. All domains conformed to the acceptable quality score (>60%) except for the Domain Applicability (48.9%). Among the six domains, Domain 'Rigour of the Development' achieved the highest mean score (83.1%). The mean quality score of the guidelines in the present study were relatively higher as compared to a previous study (Yanming et al., 2015) assessing the quality of guidelines related to Squamous Cell Carcinoma of the head and neck using the same appraisal tool. The mean domain scores of 49 guidelines as assessed by Yanming et al., (2015) ranged between 71.63% (Domain Scope of Purpose) and 32.41% (Domain Applicability) with only two domains scored above 60%, Scope of Purpose (71.6%) and Clarity of Presentation (68.1%). The inconsistencies between the two findings could be related to the exclusion of existing guidelines with low scores for the Domain Rigour of Development at the screening process of the present quality assessment. Subsequently, only higher quality guidelines were included in the complete AGREE II appraisal. This resulted in the evaluated guidelines of the present study receiving more consistent scores in the 'Rigour of Development' domain with all guidelines having scores of more than 70%.

The present study found that the domain with the lowest score was ‘Applicability’ (48.9%). This domain was the most poorly addressed by half of the eight evaluated guidelines (Gilbert et al., 2009; Wolff K-D et al., 2012; Alberta Health Services, 2014; Victorian Government, 2015). The finding is consistent with those reported in previous studies examining various guidelines using the AGREE II instrument with the scores ranging between 20.3% and 51.5% (Brosseau et al., 2014; Zhang et al., 2014; Yanming et al., 2015; Choi et al., 2015; Gagliardi & Brouwers, 2015). The other four guidelines (BKCE, SIGN, NCCN and NICE) appeared to have higher applicability scores of more than 60%.

The Applicability Domain consists of four items that assess the facilitators and barriers to guideline applications, resource implication, monitoring and/or auditing criteria and advice and/or implementation tools (The AGREE Next Steps Consortium, 2009). The lower scoring guidelines failed to sufficiently consider the facilitators, barriers, and resource implication in its implementation.

We believe that the guideline developers were more concerned with the development aspect of the guidelines rather than the discussion of important issues related to the strategy used for dissemination and implementation of a guideline. ‘Applicability’ domain is considered an important factor that is linked to the guideline uptake (Woolf et al., 1999; Shekelle et al., 1999a). The finding is of concern given much time, cost and effort are being spent developing guidelines that ultimately are not used. For a guideline to be effectively used, the conceptualization of the guideline implementation needs to be improved in the development process (The AGREE Next Steps Consortium, 2009; Huang et al., 2013). Further discussion on the implementation of the present developed guideline is addressed in the section 5.6.2.

The finding showed that the inter-rater reliability for all domains were adequate. According to minimal requirement as outlined in the AGREE II User's Manual, the appraisal involved two Dental Public Health Specialists who are experts in developing and evaluating practice guidelines.

The purpose of the quality assessment was to identify the 'high quality' guidelines that are developed using the rigorous and transparent process for adoption or adaptation as the Malaysian guidelines. The present study focused on the evaluation of the methodological quality and reporting of guidelines by using the AGREE II appraisal tool based on the rationale that high methodology quality is fundamental for credibility, reproducibility and transparency of guidelines (Simone et al., 2012; Huang et al., 2013). This is supported by findings of previous studies which indicated that evidence-based practice guidelines had statistically significant higher quality scores (Zhang et al., 2014; Yanming et al., 2015). An examination of the Anglophone guideline indicated that adherence to the methodological standards resulted in relative homogeneity in several key components of guidelines including their recommendations (Pentheroudakis et al., 2008). By applying the AGREE II instrument to the selected existing guidelines, three guidelines were rated as of good quality namely the NCCN, BKCE and SIGN (based on their overall high performance in the AGREE II appraisal). Subsequently, the NCCN, BKCE and SIGN guidelines were considered for adoption or adaptation as the Malaysian guideline for oral cancer management.

5.3.2 Currency

Guidelines will be valuable to the clinicians if they contain the most current scientific evidence (Wollersheim et al., 2005). Research on validity of practice guidelines published by the US Agency for healthcare Research and Quality (AHRQ) (Shekelle et

al., 2001b) showed that guidelines were outdated in 5.8 years. Therefore, practice guideline need to be regularly updated to ensure up-to-date information are provided to the clinician (Shekelle et al., 2001a). In producing adapted guidelines, it is important to include a means of checking the guideline currency in the development process (Fervers et al., 2006). To date, there is no validated method available for this assessment. In this present study the method for checking the guideline currency was based on the methods that was suggested in several previous literatures (Harrison et al., 2005; Graham & Harrison, 2005) and The ADAPTE Guideline Adaption Resource Kit (The Adapte Collaboration, 2009).

The currency assessment of the three aforementioned selected guidelines indicated that the NCCN and BKCE guidelines were considered current which was published in 2016 and 2014 respectively and the SIGN guidelines had not been updated for ten years. Among these three guidelines, the NCCN guideline was actively updated. Although the BKCE and SIGN guidelines were not updated recently, the peer review for update is carried out regularly. All the three aforementioned guidelines were accepted for the adaptation process because they were considered still up-to-date and relevant for use.

A systematic review that evaluated the structure and work methods of eighteen international guideline programmes indicated similar findings of which all programmes reported that they updated their guidelines occasionally. Professional organizations used more formal updating procedures than government agencies and academic institution (Burgers et al., 2003a). The possible reason for this finding may be explained by the costly and time consuming process of systematic reviews that need to be conducted for identification of new evidence (Fervers et al., 2006).

Thomson et al. (1995) and Shekelle et al. (2001a) reported several indicators for updating practice guidelines including advanced in clinical knowledge, changes in evidence, changes in local circumstance including the resources available for health care, improvements in current performance and the results of audit or evaluation. The new local guideline will be reviewed and updated (if necessary) every five years or earlier if new evidence emerges.

5.3.3 Clinical Content

All recommendations and the supporting evidence in the three selected guidelines were tabulated in a recommendation matrix. The matrix is useful in this assessment as it facilitates comparison of recommendations between the guidelines especially when more than one source guideline is being considered. Each guideline produced comprehensive recommendations that covered all aspects of oral cancer management with a number of similar recommendations found across the guidelines.

The main difficulty encountered in compiling the recommendations was the need to adapt the different level of supporting evidence used by the guidelines to a uniform scale as illustrated in Table 3.3. Due to the variation in the grading system used by the guideline developers to assess the quality of evidence and recommendations, the connection between the level of evidence and a recommendation grade could not be made. Therefore, the level of evidence was used to convey the strength of the recommendations in this guideline development process. Such information provides the user confidence that following the guideline will produce the desired health outcomes (Grol et al., 1998; Browman, 2001).

In reviewing the recommendations, almost three-quarters of the recommendations were supported with low level of evidence. Nevertheless, these recommendations are accepted as standard common practices for oral cancer management. Basically, the hierarchy of the evidence depends on the systematic analysis used to generate it. High quality systematic reviews (SRs) and randomised control trials (RCTs) are sources of high level evidence (Shekelle et al., 1999b; Grol & Grimshaw, 2003). This can be a challenge in the development oral cancer guidelines because of the limited evidence of high quality SRs and RCTs regarding oral cancer management (Daly et al., 2007).

However, strong evidence does not necessary produce strong recommendations. Apart from the quality of evidence, several factors may influence the grade of the recommendations (Shekelle et al., 1999a). For example, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) outline several factors that influence the strength of a recommendation including quality of evidence, balance between desirable and undesirable effects, patients values and preferences and costs (resource allocation) (Guyatt et al., 2008).

While the guideline development process emphasizes on the evidence-based principle, the SIGN also respects expert experiences as an input for clinical recommendation. One-third of the SIGN recommendations are based on the clinical experience of the guideline development group. For easy identification, it was classified into a different component named Good Practice Points (GPP). In the absence of evidence, clinical experience is the next respected evidence to be used to derive a recommendation (Shekelle et al., 1999b). In addition to the quality of evidence, the selection of the recommendations in the present study took into account several factors including their impact on patients care, and the applicability and feasibility of implementing them in the local context.

Complementary literature search were carried out to ensure that the current evidence pertaining to the management of oral cancer was covered in the local adapted guideline. The process of systematic review can be cumbersome and time consuming particularly in examining the overwhelming number of primary research. Therefore, the updated literature was relying on the existing systematic reviews that were published from 2015 to 2016. The approach was also applied by Andersen et al. (2014) and Gilbert et al. (2009) in adaptation of clinical practice guidelines. For the present study, only a few relevant systematic reviews were identified. As none of the findings of the systematic reviews were appropriate to be used as an update of the literature, the clinical content assessment was based solely on the existing recommendations of the three selected guidelines.

An expert panel comprising an Oral Maxillofacial Surgeon, an Oral Pathologist, an Orthorhinolaryngologist, and a Clinical Oncologist were involved in the clinical content assessment. The involvement of these interdisciplinary specialists is critical during this process to ensure the selected recommendations are valid and contextually appropriate (Green & Piehl, 2003; Linskey, 2010). (Green & Piehl, 2003; Linskey, 2010). In the present study, the expert panel consisted of the core members of the multidisciplinary team, who were directly involved in the decision making for every patient. The involvement of the non-core members is not within the scope of the present study and will be considered in the next phase of implementation of the pathway to ensure that the recommendations covers other stakeholders as they form part of the overall team in the management of oral cancer.

The panel was required to carry out an independent assessment prior to the group discussion. This process is useful as it may highlight areas of inter-professional

disagreement that may not have been evident during group discussion and to ensure that their decisions were not influenced by others in the group. The use of interdisciplinary approach in developing recommendations may enhance the credibility of the guideline in the eyes of users (Grimshaw et al., 1995a; Rycroft-Malone, 2001).

5.4 Decision on Whether to Adopt or Adapt Guidelines for Local Use

5.4.1 Consensus on the Final List of Recommendations for the Malaysian Guideline

On the basis of independent content reviews, the expert panel agreed that in general, the recommendations of the three guidelines were thorough and clearly presented. More than half (59%) of the 192 total recommendations achieved 100% agreement by the panel. The main reason for the exclusion of some recommendations is that the recommended services such as the Fluorodeoxyglucose Positron Emission Tomography-computed Tomography (FDG-PET/CT), Interstitial Brachytherapy and Sentinel lymph node biopsy are not widely available in this country.

The final list of the recommendations for the new local guideline is the result of an informal group discussion involving the expert panels. This method is useful in situations where group composition is small and consensus needs to be achieved within a shorter time (Fretheim et al., 2006). This method has been used by several guideline programmes such as Cancer Care Ontario (Cancer Care Ontario, 2012), Norwegian Guideline Panel (Kristiansen et al., 2014) and Belgian Health Care Knowledge Centre (Belgian Health Care Knowledge Centre, 2014a) in formulating their guideline recommendations. Burgers et al. (2003a) in their study found that eleven out of eighteen guideline programmes used informal consensus method to formulate recommendations.

During the group discussion, each of the recommendation was critically assessed to avoid any potential bias in selecting the most appropriate recommendations for the local guideline. The choices at this step were either to adopt or adapt existing guidelines. Commonly, adopting one guideline with all the recommendations may not be practical for some reasons. Feasibility issues such as resources, patients' ability and differences in healthcare systems may inhibit the implementation of some recommendations in the guidelines (Graham et al., 2002; Graham & Harrison, 2005). Consequently, the expert panel decided to formulate a new set of adapted recommendation by accepting 91 out of 192 recommendations from the three guidelines. Higher number of recommendations from the SIGN (n=39) and BKCE (n=35) met the requirement and were selected to be included in the new local guideline as compared to NCCN (n=19).

Although the availability Fluorodeoxyglucose Positron emission tomography-computed tomography (FDG-PET/CT) and Interstitial brachytherapy are very limited in this country, both related recommendations were included in the guideline for future consideration or as a guide for policy makers to upgrade the health care services. FDG-PET/CT is found to be useful for identification of recurrent disease and neck nodes metastases (Ord & Blanchaert, 2001; Scottish Intercollegiate Guidelines Network, 2006; Kelly et al., 2013; Lester & Yang, 2015) while brachytherapy enhanced tumour control, in the treatment of patients with early cancers (T1 and T2) with minimal toxicity experienced by the patients. Interstitial brachytherapy may be offered to early stage patients who refused surgery (Mazeron et al., 1990; Harrison, 1997). However, the Sentinel lymph node biopsy was excluded because its usefulness in Malaysia is still lacking for the reason that more than half of oral cancer presented at advanced stages (Manan et al., 2016).

5.4.2 Modifications of the Recommendations

Modifications were made to several recommendations to fit with the existing local health care system. These included recommendations 1.3(c): Biopsy, 1.4: Conventional imaging of the primary tumour, 1.8: Human Papillomavirus (HPV) Testing, 1.9.2: Primary site reporting, 2.1: Multidisciplinary involvement, 2.2.1: Dental evaluation, 2.3.3: (g) Advanced stage of oral cancer (Stage III and IV) and are discussed in the following sections. The modifications were supported with research evidence or expert opinion (through consensus) in the absence of research evidence. According to Irwin and Peppercorn (2012) the development of the guideline should be specifically tailored for a given clinical practice in order to enhance its' uptake by the target users. It has been widely mentioned in the literature that guidelines are more likely to be used if the recommendations are compatible with the existing values and routine, and scientific evidence was explicitly described in the guideline (Grol et al., 1998; Foy et al., 2002; Burgers et al., 2003b).

5.4.2.1 Recommendations 1.3 (a): Biopsy and 1.9.2: Primary Site Reporting

Biopsy is one of the important components in diagnosis and staging of oral cancer. Biopsy should provide sufficient information in order to determine the status of the lesion (Neville & Day, 2002; Macey et al., 2015; Carreras-Torras & Gay-Escoda, 2015). In addition to reporting of the tumour localization, tumour histology, tumour grade, depth of invasion, lymphatic, vascular and perineural invasion as listed in the recommendation 1.3 (a) Biopsy of BKCE guideline (Belgian Health Care Knowledge Centre, 2014a), analysing and reporting of the invasion pattern (cohesive or non-cohesive) in diagnosis and staging of early-stage oral squamous cell carcinoma was also

recommended by the expert panels based on the current literatures by Li et al. (2013) and Almagush et al. (2015).

Both literatures that evaluated the worst pattern of invasion (WPOI) of patients with early-stage oral tongue cancer (cT1-T2N0) revealed that WPOI is a strong pathological mortality, with the hazard ratio (HR) of 2.34, 95 % CI 1.26–4.32. Li et al., (2013) reported the WPOI would significantly predict the locoregional recurrence for the patients with HR of 3.63 (95 % CI: 1.56-8.47).

5.4.2.2 Recommendation 1.4: Conventional Imaging of the Primary Tumour

Computed Tomography (CT) scans are routinely used to assess the extent of the primary tumour invasion, regional lymph nodes status or metastases to the neck (Pigadas & Jevon, 2014; Lester & Yang, 2015). The expert panel decided to include CT of thorax, abdomen and pelvis also especially if the patient is undergoing CT for primary oral cancer (in the recommendation 1.4: Conventional imaging of the primary tumour). This is consistent with the information reported by Arya et al. (2014) which stated that CT has a valuable role to rule out pulmonary metastases in higher T stage cancers and CT of the abdomen is indicated for patients with high clinical index of hepatic metastases.

5.4.2.3 Recommendation 1.8: Human Papillomavirus (HPV) Testing

To date, there is no evidence from randomized control trials (RCT) that HPV status of a head and neck tumour has an important role in treatment decisions. As both subtypes Human papillomavirus HPV (HPV 16 and HPV) are related to oropharyngeal and oral cancer (Termine et al., 2008; Dayyani et al., 2010; Carreras-Torras & Gay-

Escoda, 2015), the routine testing for Human Papillomavirus (HPV) (recommendation 1.8) was changed to HPV testing based on the expert opinion. This is meant to exclude both HPV 16 and HPV 18 as routine diagnostic tests for oral cancer patients.

5.4.2.4 Recommendation 1.2: Multidisciplinary Involvements

The recommendations stated in section 2.1: Multidisciplinary involvements from the three guidelines were combined for the purpose of developing a local multidisciplinary team (MDT) with sufficient number of specialists for the management of oral cancer patients. Currently, there is no standard model for the composition of a multidisciplinary team. The composition of the team would depend on the type of cancer, the services needed and patients' preferences (Westin & Stalfors, 2008). Although all team members, for example as outlined in the NCCN (National Comprehensive Cancer Network, 2016) are necessary for the management of oral cancer, it is difficult to get all these specialists together at the same time. The expert panel suggested the concept that patients will be attended by a core team of which should comprise the specialist disciplines of Oral and Maxillofacial Surgery, Otorhinolaryngology, Pathology, Clinical Oncology, Radiology, Plastic and Reconstructive Surgery. Patients will be then referred to the non-core team (based on need) which comprise of the General Practitioner, Dentist, Nursing Care, Speech and Swallowing Therapist, Nutritional Therapist and Psychosocial Worker. The suggested MDT composition is compatible to those listed in other literature (Ord & Blanchaert, 2001; Taylor et al., 2010).

5.4.2.5. Recommendation 2.2.1: Dental Evaluation

Evidence shows that patients with head and neck cancer are at risk of post radiotherapy complications including radiation induced dental caries, tooth loss and periodontal loss attachment (Epstein et al., 2001; Denis et al., 2003). Dental or oral management including effective pre-treatment evaluation can help decrease dental caries and other associated problems (Chang et al., 2007; Epstein et al., 2012; Moore et al., 2014). As each recommendation of the guidelines on dental evaluation carries essential information for patient management, the three recommendations were combined into one meaningful recommendation.

5.4.2.6 Recommendation 2.3.3 (g): Advanced Stage of Oral Cancer (Stage III and IV)

Interrupting and prolonging a course of radical radiotherapy should be avoided because the overall treatment time is found to be associated with the patients' outcomes. After taking into consideration the implementation issues such as contextual factors, logistical, and resource available locally, modification was done on the overall treatment time (interval between surgery and the end of postoperative radiotherapy). Instead of an overall treatment time of '10-11 weeks', the panel decided to modified the treatment time to 'should not exceed_14 weeks' for the recommendation in section 2.3.3 (g) Advanced stage of oral cancer (Stage III and IV). The overall treatment time recommended by the experts panel is comparable with the finding of a review by Langendijk et al. (2010) which reported a 5-year loco-regional tumour control rate on more than half (60%) of the patients treated within a total treatment package (TPP) of 11-13 weeks. Rosenthal et al. (2002) in their study showed that package time of 100 days or less in the treatment of patients with Squamous Cell Carcinoma of Head and

Neck Cancer was a strong predictor of better 3-year survival ($p=0.021$) and locoregional control ($p=0.13$).

5.4.3 Draft Guideline

The draft covers all aspects including the development, implementation and evaluation of the guideline. Following the adaptation framework PGEAC by Graham et al. (2003), the methods used and the supporting evidence is explicitly explained in the draft guidelines to show that the guideline has been developed through a rigorous and evidence-based process. An algorithm that outlined a comprehensive picture of patient management is presented in the guidelines. According to Browman (2001), the use of an algorithm as a companion document for a comprehensive guideline may facilitate its use by the clinician. Clinical audit indicators were provided in the guideline for the purpose of evaluating and monitoring the quality of the guideline. The quality of the draft was verified by the supervisors of the research project before being reviewed by the group of multidisciplinary specialist as discussed in the following section.

5.5 The Multidisciplinary Specialists' Feedbacks Regarding the Draft Guidelines for Oral Cancer Management in Malaysia

5.5.1 Group Composition

The involvement of multidisciplinary specialists in reviewing the draft guidelines and reaching a consensus (by conducting Focus Group Discussion (FGD)) was crucial as this approach allows for a systematic and transparent development of practice guideline. According to Shekelle et al. (1999a), at least three disciplines need to be involved in reviewing the draft guideline including 1) an expert in clinical content, who can review the content of the recommendations, 2) a methodological expert, who can

review the method used in the development process and 3) the potential users of the guidelines, who can judge the applicability of the guideline. Moreover, engaging potential users in this process may increase the awareness about the guideline and improve the guideline adherence, thus facilitating smoother implementation.

In the present study, the Focus Group Discussion (FGD) involved clinical specialists who are experienced in managing oral cancer patients in Malaysia and also the potential target users of the guidelines. The group comprised five Oral Maxillofacial Surgeons, one Oral Medicine and Oral Pathologist, and one Dental Public Health Specialist. The Dental Public Health Specialist was involved based on her experience in guideline development and could verify the methodological aspect of the local guideline. Five specialists who initially agreed to participate in the FGD, were unable to attend the FGD eventually. Nevertheless, the group composition was considered appropriate with all the relevant disciplines represented in the FGD (Jones & Hunter, 1995).

The non-dental specialists and patients were not involved in the FGD because the involvement of too many disciplines and also patients would have complicated the process of FGD. We feel that the involvement of non-dental personnel such as the Otorhinolaryngologist, and Clinical Oncologist were more appropriate in the content analysis to obtain their expert judgment on which recommendations to be adapted for local use. Previous literature suggested that patients view and their preference should be taken into account during the development process (Grimshaw et al., 1995a; Faggion, 2013). However, we perceived that it was not appropriate to have patients and the specialists in the same group because the patients may not understand the clinical and technical aspects of the discussion, and thus would feel inhibited to actively contribute in the FGD process. As suggested by Grimshaw et al. (1995a), this issue could be

overcome by seeking feedback from patients or representative of their organisations regarding the usefulness of the guideline during the implementation phases.

5.5.2 Feedback Regarding the Draft Guidelines

Generally, positive feedbacks were received from the participants regarding the draft guideline. The participants were satisfied with the overall structure of the draft. Only a few comments were received for Section 1 (Introduction) and Section 2 (Development of the guideline), related to spelling error and the composition of the target users.

Overall, the content of the discussion was mostly focused on Section 3: Clinical recommendations. Most of the discussion was related to some recommendations that needed clarification and rewording while offering some constructive comments on certain aspects of Section 3. These comments are discussed below according to specific interventions including 1) diagnosis, 2) treatment, 3) follow-up care (please refer to Table 4.12 for numbering of the recommendations), 4) summary of the evidence and 5) concerns of the participants.

1) Diagnosis

Patient Information and Consultation in Decision Making

Recommendation 1.1 stating that *the patient must be kept fully informed about his conditions, treatment options, and consequences. Patient preferences should be taken into account when deciding on a treatment option.* With regards to this, few participants had trouble informing the patients about their conditions in certain circumstances due to family members' interference. Some family members feared that the disclosure of

cancer diagnosis may harm the patients (especially their elderly parents) and they were worried that their parents would not be able to cope with the bad news.

The participants' feedback is contrary to that reported in previous literature whereby most cancer patients want to have as much information about their condition as possible including the possible treatments and even the prognosis of the disease. Furthermore, they wish to be actively involved in the decisions about their own care. In relation to the multidisciplinary concept, the treatment plan was considered incomplete in the absence of patients' input within the working team (Jefford & Tattersall, 2002; Cox et al., 2006).

Generally, patients need to be well informed for them to cope not only with the initial diagnosis of cancer but also with the procedures and options for treatment. This is supported by the finding of previous studies which showed that the provision of information may improve patients' compliance, satisfaction, clinical outcomes and quality of life (Greenfield et al., 1985; Fallowfield, 1997). The surgeons need to consider the importance of patient's right and their role in decision-making, regarding their care. They have no choice, but to inform the patient about the diagnosis.

The Accuracy of Biopsy and Histopathological Finding

Tissue biopsy and histopathological examination remains the best diagnostic test for Oral Squamous Cell Carcinoma. The biopsy assesses the severity of epithelial dysplasia which is one of the most important prognostic indicators of malignancy through histological examination and categorization of the tumour (Neville & Day, 2002; Macey et al., 2015; Carreras-Torras & Gay-Escoda, 2015).

With regards to the recommendation 1.3: Biopsy and 1.9.2: Primary site reporting, the pathologist repeatedly emphasized that the biopsy and excised specimen should be taken adequately including the location and depth of the tumour in order to get accurate histopathological results. For optimum tumour control, it is important to ensure that the margins and the depth of tissue resected must be disease free. Literature states that if the excision is made with a cold scalpel, a one mm safety margin should be considered, but if it is made with a CO2 laser, safety margins should be extended even to the 5mm to ensure the excision is considered complete (Cercadillo-Ibarguren et al., 2010; Wolff K-D et al., 2012).

Although an argument existed on the best management for inconclusive diagnosis, it was agreed upon that the management should follow the recommendation in the guideline. The biopsy should be repeated if the result is inconclusive and the tumour is suspect. In certain circumstances, particularly when patients are referred to another centre for further management, it was agreed upon that the surgeons could ask for another diagnosis confirmation before proceeding with the treatment plan if the pathology and clinical findings do not match. Based on this discussion, the recommendations 1.3 (a) and 1.3 (b) remained as it is.

In relation to the recommendations 1.9.2: Primary site reporting, the surgeons should be provided with complete histological assessment for them to accurately classify the grade of the tumour. Apart from complete histological features, the report should include some other prognostic factors such as tumour thickness, an extra-capsular spread of nodal metastases and pattern of invasion (Kerawala et al., 2016). Based on the dataset for Histopathology Reporting of Mucosal Malignancies of the Oral Cavity by The Royal College of Pathologists (Helliwell & Woolgar, 2013) it was found that all data required for histopathological reporting was covered in the recommendation. The

comments from the participants also prompted a removal of P16 and R status from the histology assessment due to insufficient evidence.

2) Treatment

In this section, the recommendations were categorised according to the stage of disease to facilitate reading and identification of the related intervention for specific groups of patient. Participants commented that most of the recommendations were already in practice except for some added information needed on certain recommendations to make them more explicit. Several issues were brought up during the discussion including the primary radiotherapy procedure in the management of early stage of oral cancer and management of neck lymph nodes which is further discussed as follows.

Primary Radiotherapy Procedure in the Management of Early Stage of Oral Cancer

The participants commented that the recommendation on primary therapy for patients who refused surgery need to be added in the management of early stage of oral cancer (Recommendation 2.3.2). Generally, the curative treatment for early stage disease (T1-T2, N0) is either surgery or radiotherapy. Based on Brown and Langdon (1995), the choice for surgery or radiotherapy as a primary modality might be influenced by several factors including the site of the primary tumour, stage of the disease, conditions and preference of the patients. Commonly, surgery was preferred by the participants for small tumours particularly T1 of which the surgery performed rarely caused any deformity in form and functions. However, in some instances where patients refused surgery or those who were concerned about the preservation of form and functions, for example, lip cancer, primary radiotherapy may be offered to them.

The related literature mentioned that the morbidity and functional outcome of each method should be considered in determining the appropriate treatment modality for each patient. However, the choice of treatment greatly depends on the patients' preference since both modalities produce a similar outcome in terms of survival, but differences in the complication of the treatment (Henk & Langdon, 1994). In reviewing the recommendation, it was found that the information has been included in the recommendation 2.3.2 (e). Subsequently no additional recommendation was done for the management of early stage of oral cancer.

Management of neck lymph nodes

Although participants were generally in favour of the recommendation 2.3.4 (b) which stated that *perform a selective neck dissection of at least level I, II and III in all patients with a cNOMO oral cavity SCC that is treated surgically*, they suggested certain parameters that need to be taken into account such as site, grade, pattern of invention, lymphatic infiltration and choice of reconstruction prior to performing the procedure. Their feedback was consistent with the previous literature which reported similar indicators for selective neck dissection that mainly depends on the risk of disease spread to the different level of the neck (Ebrahimi et al., 2012).

3) Follow-up care

Follow-up Schedule

Recommendation 3.1 that outlined the follow-up schedule for each patient drew feedbacks from the participants. They argued that the follow-up frequency is different from the current practice. They preferred to review patients more frequently because most of their patients presented at stage III and IV and were considered at high risk of

tumour recurrence of metastases (Shah & Gil, 2009). To date, there is no evidence to support a specific time-frame for follow-up. The follow-up frequency followed by the participants is based on the knowledge acquired during their training. Subsequently, the frequency of follow-up was modified based on the current practice.

Psychosocial Support

The feedback on recommendation 3.5 regarding the psychosocial support reflected the importance of the service to optimise the quality of life of cancer survivors and the need for a clinical psychiatrist to be in the core team of patient management. The management of a cancer patient does not end with the completion of the treatment. The lifelong treatment complications experienced by the patient may increase the risk for psychological disorders.

Participants feedback was supported by the evidence of several studies which showed that cancer patients are prone to have a psychological disorder as compared to those with chronic illness (Evans et al., 2005). Other studies reported the increased rate of suicide among long-term cancer survivors (Beard et al., 2013) and depression is found to be associated with increased risk of cancer death (Satin et al., 2009).

This evidence highlighted the importance of availability and accessibility of supportive services in preventing or reducing the psychological problem among cancer patients (Andersen et al., 2014). A surgeon should have the minimum knowledge for the assessment of psychological symptoms and refer patients to the psychiatrist or psychosocial workers when necessary. As the services are already congested in certain local hospitals, specific criteria need to be considered in referring such patients in order to ensure that all needy patients will have the access to support care services.

4) Summary of the Evidence

Imaging of neck lumps and nodes.

In reviewing the Role of Computed Tomography (CT) in the imaging of neck lumps and nodes, a participant suggested adding evidence related to the accuracy of CT in detecting neck metastases. Although it has been widely mentioned in the literature that CT is routinely used to determine the extent of the primary tumour, invasion, regional lymph nodes status and distant metastases disease, the reliability of CT in the assessment of neck nodes should always be treated cautiously. It needs to be confirmed with histopathological assessment which has been found to be a more reliable method of diagnosing cervical metastatic disease (Pigadas & Jevon, 2014; Lester & Yang, 2015).

The participants' comments were based on the study by Woolgar et al. (1994) in a series of 86 patients presenting with oral cancer who underwent neck dissection as a follow-up of preoperative staging by palpation under general anesthesia and CT imaging. The detailed histopathological assessment revealed the incidence of about one-quarter false negative among cases with a clinically negative neck. Moreover, extranodal spread of metastatic carcinoma was detected in less than one-fifths among clinically negative necks. The participants' comments lead to an addition of this information as supporting evidence for the imaging of neck lumps and nodes.

Surgery

The statement *in considering reconstruction, it must be considered that a distance of less than 1 mm between the histologically demonstrated tumour margin and the resection line counts as a positive margin of resection* supporting the recommendation for surgery attracted the participants' attention to further discuss it. The statement

seemed contradictory to the current practice. According to the statement, the plan for reconstruction is based on the histological tumour margin. On the contrary, the construction is carried out immediately after a surgery whether the margin is clear or not. The participants thought that the statement is more related to the success indicators for a surgery, rather than reconstruction.

The participants' comments are consistent with that recommended in other studies as 'adequate surgical margin' for oral and oral pharyngeal carcinoma. The studies indicated that 5 mm or more is considered as safe margin, 3 mm or less as close margin and less than 1 mm as involved margin (Woolgar & Triantafyllou, 2005; Nason et al., 2009). Nason et al. (2009) found that patients with margins of 5 mm or more had a 5-year survival rate of 73% when compared to those with margins of 3 to 4 mm (69%). Consequently, the term *in considering reconstruction* was placed by *for optimum tumour control*.

5) The Concerns of the Specialists

Based on participants' experiences a lot of their patients were diagnosed at late stage. Late presentation is considered an important issue in oral cancer management because advanced stages tumour requires more extensive procedures and are associated with poor prognosis (Wazir et al., 2015). Evidence showed that five years survival rate for patients with stages III and IV was only 20% as compared to 80%-90% among patients with early disease (Viviano et al., 2013; Pigadas & Jevon, 2014).

This situation is quite commonly seen in this region (Warnakulasuriya, 2009). Kerdpon and Sriplung (2001), in their study among 161 oral cancer patients in Thailand found that 61.5% were diagnosed with advanced stage disease. Meanwhile, Wazir et al.

(2015) study on 161 oral cancer patients in Peshawar found that 50 % of them had a delay in diagnosis of more than 150 days. Three-quarters of the patients with the delay in diagnosis were reported at stage IV.

Through the participants' observation, seeking alternative therapy is the most important contributing factor for the delay in diagnosis among the local patients. They tended to use alternative medication before or along the treatment phases and ultimately sought professional help with advanced stage disease. The participants' feedback is correlated with the finding of Kerdpon and Sriplung (2001), where they found that having herbal medication before health care professional consultation significantly increased the risk of advanced stage of Oral Squamous Cell Carcinoma (OR 5.77; 95% C.I. 1.25-26.62). The role of media in advertising alternative products poses a great challenge to the health care providers in convincing the public regarding the importance of early diagnosis that contributes to successful treatment outcomes.

5.6 Finalising the best practice guidelines.

5.6.1 Final version of the best practice guidelines.

The comments and feedback from the panel are used to improve the draft guideline. The final guideline as shown in Appendix Q does not involve any change to the structure and format as the multidisciplinary specialists agreed that the draft was well organised and all required information are available. In response to the panel comments, minor changes were made on certain recommendations and segments of the draft as outlined in the section 4.5 to make the statements more explicit and specific for a given intervention.

One recommendation related to 2.4 (g) Tumour downstaging for treatment of very advanced-stage oral cancer were added based on the multidisciplinary specialist group's experiences and consensus achieved among the members. The "Standard, Option and Recommendation" Project of the French National Federation of Cancer Centres (FNLCC) (Browman, 2001) and The SIGN Guideline Development Program (Scottish Intercollegiate Guidelines Network, 2015) also included clinical experience as input in the development of their recommendations based on the feedbacks and consensus achieved among the experts.

The final guidelines need to be approved by the Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAs) before dissemination to the relevant target groups (Ministry of Health Malaysia, 2015). Dissemination may also include publication of the guideline document or portions of the guideline in a relevant journal.

5.6.2 Implementation

Various strategies have been used to implement guidelines and it differed according to guideline programs (Burgers et al., 2003a; Grimshaw et al., 2004b). Simple dissemination of practice guideline or through a publication in a scientific journal is likely to have less impact to guideline use (Irwin & Peppercorn, 2012). There are certain issues that need to be taken into account when implementing a particular guideline including the barriers and facilitators to implementation, strategy to increase uptake and resource implications of applying the guideline locally (The AGREE Next Steps Consortium, 2009; Alonso-Coello et al., 2010)

It is important to identify any barrier before conducting an implementation strategy. Literature has shown that a lack of awareness, attitude or acceptance of the clinicians,

recommendations demanding new knowledge or extra resources and complex format of the guidelines are among barriers to clinician adherence (Grol et al., 1998; Grol, 2001; Grol & Wensing, 2004; Gagliardi & Brouwers, 2015). A local study assessing the implementation strategies of the Ministry of Health guidelines on oral health revealed that lack of adequate manpower resources, lack of clinical leadership and lack of infrastructure were the main barriers to the guidelines implementation (Jaapar, 2009).

Engaging specialists who are experienced and currently managing oral cancer patients in the FGD is one of the implementation strategies in this study for seeking feedback regarding the new developed local guideline (including facilitators and barriers) from the major stakeholders and to develop ownership to the resulting guideline. Generally, the specialists showed a positive attitude toward accepting the guideline.

The local guideline produced is comprehensive in its attempt to cover all aspects of oral cancer management. Clinicians may find difficulty to identify some information or recommendations pertaining to a specific intervention. An algorithm was provided in the Malaysian guideline to facilitate quick reading and understanding, and easier implementation of the recommendations. The benefit of an algorithm as an effective implementation tool has been illustrated in previous literatures (Irwin & Peppercorn, 2012; Gagliardi & Brouwers, 2015).

There should be a means of evaluating the effectiveness of guideline implementation. The application of the guideline in practice is expected to have several potential benefits to the patients and improve the quality of care (Thomson et al., 1995). Studies measuring the effects of guidelines predominantly focused on both the process and structure of care and patient outcomes. Patient survival and quality of life are important

outcomes that need to be considered in evaluating the impact of the guideline utilisation (American Society of Clinical Oncology, 1996).

Audit and feedback on performance may be valuable in assessing whether the guidelines have been adhered (Thomson et al., 1995). During the FGD the specialists proposed two clinical audit indicators for quality management including 1) monitoring the follow-up protocol, 2) treatment time from surgery to completion of radiotherapy. This is in line with the method used by the BKCE and SIGN guideline in monitoring the quality of care after implementation of their guidelines (Scottish Intercollegiate Guidelines Network, 2006; Belgian Health Care Knowledge Centre, 2014a).

Judgment about what kind of resources available in the country and feasibility of interventions for implementation has been taken into account during the development process. As this guideline is meant to be utilised in the existing Malaysian system, no additional resources are needed in order for this guideline to be implemented.

5.7 Limitation

The present study employs a combination of reviewing high quality evidence and a qualitative approach to obtain feedback, refinement and agreement from a multidisciplinary group in developing a best practice guideline for oral cancer management in Malaysia. However, a few limitations have been identified for this study as follows:

1. The guideline search was limited to guidelines published in English. This could have introduced bias in the selection process as some of the relevant guidelines may not be included in this study. However, as English is widely used worldwide, the

present study had managed to cover a wide range of databases and website for the last sixteen years which might increase the validity of the findings.

2. This study does not incorporate patients' perspective in guideline development. Ideally, all relevant disciplines including patients should be involved during the development process in order to enhance the quality of the guideline produced. This issue may be overcome by seeking patients' feedback during the implementation phases.
3. The quality assessment only involved two appraisers. As the appraisal process is cumbersome and time consuming, recruiting more appraisers and even sustaining involvement of the appraisers in the assessment was difficult. The specialists had to be reminded and encouraged to complete their assessment within the stipulated time despite their busy schedules. It should be noted however that the two appraisers are methodological experts in guideline development at the Oral Health Division, Ministry of Health Malaysia and therefore were very proficient in undertaking the task.
4. The literature review for this study was assessed only by author. The use of multiple reviewers would have enhanced the validity of this process. In order to overcome this limitation and to strengthen the validity of the work process, the selection of the recommendations was carried out by an interdisciplinary expert panel with the final guideline being resolved by a group multidisciplinary specialists who are experienced in managing oral cancer patients and guideline development.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Based on the objectives of this study, it can be concluded that:

1. Three out of fifteen existing guidelines (identified from a review of literature) were considered the most appropriate for adoption or adaptation in the development of Malaysian guidelines for oral cancer management. These include the NCCN, BKCE and SIGN. The three guidelines were selected based on their overall high performance in quality assessment using the AGREE II instrument. According to the currency assessment, the NCCN, BKCE and SIGN were still considered up-to-date and relevant for use. Based on the content analysis of the 192 total recommendations that was extracted from the three aforementioned guidelines, 12% of the recommendations were supported with high level evidence, 73% were supported with low level evidence and 33% were based on expert experience (GPP). Sixty percent of the recommendations achieved 100% agreement by the expert panels through an independent assessment. The complementary literature search (2015-2016) revealed that none of the findings of the systematic reviews were appropriate to be used as an update of the literature.
2. Based on the informal group discussion among the expert panel, 91 recommendations from the three existing guidelines were accepted for inclusion into the Malaysian guideline. Eighty one recommendations were accepted by the panel without any modification whereas three were modified based on the suggested evidence and one was modified based on expert opinion. Six recommendations were combined to form two recommendations. One new recommendation was added to the local guideline. The draft version of the guideline comprised three sections

(Section 1: Introduction, Section II: Development of the Guideline and Section III: Clinical Recommendations) and an algorithm on the whole process of oral cancer management.

3. The multidisciplinary specialists involved in the Focus Group Discussion agreed that the structure of the draft guidelines was well organized and all information required were available. Only a few comments were received for Section 1 (Introduction) and Section 2 (Development of the Guideline) related to spelling errors and the composition of the target users. In reviewing Section 3, some comments were received from the specialists which stated that 1) twelve recommendations needed clarification and rewording, 2) some parameters needed to be added to the recommendation 2.3.4 (b): Management of neck lymph nodes, 3) an additional recommendation was needed which related to section 2 (g) tumour downstaging for the treatment of very advanced-stage disease, 4) information on the accuracy of the CT was needed in the summary of evidence for imaging of neck lumps and nodes and 5) some improvement needed in the layout of the algorithm.
4. The 47-pages Malaysian guideline which covers all aspects of oral cancer management from diagnosis through treatment until follow-up care was formatted based on the feedback of the multidisciplinary specialists. The final guideline consists of three sections as in the draft, an algorithm, and clinical audit indicators for quality management for the purpose of evaluation and monitoring the guideline implementation. The Malaysian guideline has been developed with rigour in order to better guide clinical decision making by healthcare professionals in managing oral cancer patients in this country.

6.2 Recommendations

1. The final guideline needs to be approved by the Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAs) prior to dissemination to the relevant target groups.
2. The Malaysian guideline should be made widely available to all potential target users in order to facilitate its implementation. However, simple dissemination of the printed documents is likely to have less impact on clinical practice. Therefore, it needs to be accompanied with other effective implementation strategies such as developing a quick reference for the professional and patient information leaflets, and educational interventions by local coordinators. Help can be sought from MaHTAS to disseminate the guideline to all public healthcare facilities including uploading it onto the websites of the Ministry of Health or relevant professional societies for greater accessibility.
3. Patients' views and preferences should be taken into account during the implementation phases of this guideline. This could be carried out through a future study to obtain feedback from the patients regarding the usefulness of the guideline.
4. Beside clinical audit indicators proposed by the specialists to be used in monitoring the adherence of the guideline, future study should look into the effectiveness of the guideline implementation and its impact on the process of care and patients' outcome (survival and quality of life).
5. A review of this new Malaysian guideline should be conducted at least every five years or earlier in order to update new emerging evidence for surgeons. When updating the guidelines, the importance of supportive care in the pre-treatment

assessment and follow-up care could be delved further to provide holistic and total care to the patients. This is because supportive care is an essential component in the management of oral cancer, not only to assist patients in coping with treatment complications but also in their initial diagnosis of cancer and during the subsequent treatment phases.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

1. Poster presentation at the 16th Annual Scientific Meeting of IADR Malaysian Section on 18.03.2017 at Hotel Armada Petaling Jaya, Selangor.

Title: Guidelines for oral cancer management: A systematic assessment of quality using the AGREE II Instrument.

2. A submission of manuscript entitled “Assessment of the Quality of Guidelines for Oral Cancer Management Using the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument” to a Tier 1 ISI Journal- Health Policy Journal on 1.08.2017.

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