COST-EFFECTIVENESS OF MOBILE PHONE IMAGING TELEDENTISTRY (MPIT) FOR EARLY DETECTION OF ORAL CANCER IN MALAYSIA: A MARKOV DECISION ANALYSIS APPROACH

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by

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ACTION	ASEAN Costs In Oncology study
AJCC	American Joint Committee on Cancer
ASR	Age-standardized rate
CHE	Catastrophic health expenditures
COE	Conventional clinical oral examinations
C1	COE via high-risk community screening camps
C2	COE in primary dental clinics
CPI	Consumer price index
CRM	Cancer Research Malaysia
CUA	Cost-utility analysis
EQ-5D	EuroQol 5-dimensional questionnaire
EQ-5D-5L	Five-level EuroQol five-dimensional questionnaire
EQ-VAS	EuroQol visual analogue scale
FACT-H&N	Head and Neck Functional Assessment of Cancer Therapy
HRQoL	Health-related quality of life
HTA	Health technology assessments
HTAR	Hospital Tengku Ampuan Rahimah
HUS	Hospital Umum Sarawak
ICD-10	International Classification of Diseases, 10th revision
ICER	Incremental cost-effectiveness ratio
M	Mean
MOE	MeMoSA® for oral examination
M3	MOE in primary clinics (at targeted high-risk communities)
M4	MOE in primary dental clinics
M5	MeMoSA® as referral tools only in primary dental clinics
M6	MOE in primary medical clinics
M7	MOE by patients
MOH	Ministry of Health Malaysia
MPIT	Mobile Phone Imaging Teledentistry
MTR	Malignant transformation rates
MYR	Malaysian Ringgit

NCI	National Cancer Institute
NMB	Net-monetary benefit
OOP	Out-of-pocket
OPMD	Oral potentially malignant disorders
OSCC	Oral squamous cell carcinoma
PAF	Population attributable fraction
PLI	Poverty line index
QALY	Quality-adjusted life years
QOL	Quality of life
RCT	Randomized controlled trials
SD	Standard deviation
THB	Thai Bhat
USD	United State Dollar
WHO	World Health Organization
WTP	Willingness-to-pay

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KEBERKESANAN KOS TELEPERGIGIAN MELALUI PENGIMEJAN TELEFON MUDAH-ALIH UNTUK PENGESANAN AWAL KANSER MULUT DI MALAYSIA MELALUI SIMULASI MARKOV

ABSTRAK

Walaupun banyak inisiatif saringan kanser mulut dilakukan, kebanyakkan pesakit masih didiagnosis pada tahap yang lanjut. Ini memberi kesan sosial dan ekonomi yang besar. Untuk mengatasi cabaran ini, suatu aplikasi baru bernama MeMoSA® dikembangkan dengan menggunapakai medium telepergigian melalui pengimejan telefon bimbit untuk pemeriksaan lesi dalam mulut (MOE). Aplikasi ini berfungsi sebagai platform komunikasi antara pengamal kesihatan primer dengan pakar yang berada di luar lokasi. Kajian ini bertujuan untuk melaporkan keberkesanan kos MOE, untuk menyaring pesakit dengan lesi di dalam mulut yang berpotensi menjadi malignan (OPMD) dan kanser mulut berbanding dengan pemeriksaan oral secara konvensional (COE) yang dilakukan secara rutin melalui kem bergerak ke komuniti berisiko tinggi (C1) atau di klinik pergigian (C2). Perspektif sosial digunakan dalam analisa untuk merangkum semua kesan jangka panjang pengesanan awal kanser mulut. Analisa dijalankan melalui model Markov yang mensimulasikan kesan pelbagai strategi penyaringan MOE pada kos dan kualiti hidup yang diselaraskan dengan jangka hayat (QALYs) untuk kohort 100,000 orang dewasa berusia 40 tahun. Dapatan daripada dua fasiliti kesihatan tertiari menunjukkan kanser di tahap yang lanjut menyumbang kepada kos perkhidmatan dan perbelanjaan isi rumah yang tinggi, di samping pengurangan kualiti hidup, berbanding dengan tahap awal dan OPMD. Hasil simulasi membuktikan bahawa implementasi MOE di pusat-pusat sasaran terpilih di kawasan luar bandar (M3) mampu menjimatkan kos sebanyak MYR

120,711 untuk penjanaan QALY yang sama seperti strategi C1. Begitu juga, nisbah keberkesanan kos tambahan (ICER) yang dikira membuktikan bahawa implementasi MOE oleh doktor gigi (M4; MYR 3,792) dan pengamal perubatan am (M5; MYR 7,706) adalah adalah kos efektif lebih daripada 97% berbanding dengan C2. Strategi M4 mampu mengesan lebih banyak pesakit dan meningkatkan kualiti hidup mereka berbanding strategi C2 sambil kekal kos-efektif, walaupun jika terdapat peningkatan dalam kadar insiden atau rujukan pesakit. Analisis sensitiviti sehala turut menunjukkan strategi M4 masih kos-efektif pada semua julat nilai yang digunakan, dengan insiden OPMD dan sensitiviti doktor gigi menunjukkan variasi yang terbesar. Sebaliknya, pelaksanaan MOE untuk rujukan pesakit yang positif sahaja (M6) dan untuk pemeriksaan mulut sendiri oleh pesakit (M7) dianggap tidak kos-efektif kerana menjana jumlah QALY yang kurang dan pada kos yang lebih rendah berbanding C2, iaitu masing-masing pada MYR 71,082 / QALY dan MYR 24,572 / QALY. Kos pulang modal untuk satu pembelian MeMoSA® ialah MYR 9.90 dan MYR 9.30 masing-masing pada tahun pertama dan berikutnya. Kesimpulannya, data semasa menunjukkan MeMoSA® melalui pendekatan M3, M4 dan M5 adalah strategi yang kos-efektif.

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ABSTRACT

Although numerous national oral cancer screening initiatives are carried out in Malaysia, patients are still being disproportionately diagnosed at later stages, leading to substantial social and economic burdens. To overcome these challenges, a novel application called MeMoSA® was developed by incorporating a mobile phone imaging teledentistry for oral examinations (MOE). The application serves as a communication platform between primary healthcare practitioners and specialists located off-site. This study aims to report the cost-effectiveness of MOE, for screening patients with oral potentially malignant disorders (OPMD) and oral cancer compared to the conventional oral examination (COE) conducted routinely via either high-risk community screening camps (C1) or primary dental clinics (C2). A societal perspective was adopted to encompass all the far-reaching consequences of early detection of oral cancer. A Markov modeling was applied to simulate the impact of various MOE screening strategies on cost and quality-adjusted life-years (QALYs) for a hypothetical cohort of 100,000 adults aged 40 years. The initial findings from two tertiary healthcare centers demonstrated that late-stage oral cancer incurred significantly higher healthcare provider and patient household costs, in addition to a lower quality of life compared to the early stage and OPMD. Model simulations with these values evidenced that MOE in targeted primary clinics in high-risk communities (M3) incurred lesser societal costs by MYR 120,711 to generate similar total QALYs as C1. Additionally, the incremental cost-effectiveness ratio (ICER) calculated

evidenced that MOE by both dental practitioners (M4; MYR 3,792) and general medical practitioners (M6; MYR 7,706) was cost-effective more than 97% of the time when compared to C2. At a higher incidence and self-referral rates, the M4 strategy was able to detect more patients and improve their quality of life relative to C2, while remaining cost-effective. A one-way sensitivity analysis of the primary M4 strategy demonstrated that it was cost-effective throughout all the value ranges, with incidences of OPMD and sensitivity of dentists producing the largest variations. On contrary, the implementation of MOE for referrals of positive screen patients only (M5) and for mouth self-examination by patients (M7) was deemed not cost-effective as they generated lower total QALY and lower societal costs relative to C2, at MYR 71,082/QALY and MYR 20,022/QALY respectively. The breakeven cost for one-of-purchase of MeMoSA® was MYR 9.90 and MYR 9.30 in the first and following years respectively. In conclusion, the current evidence projects MeMoSA® via M3, M4 and M6 approaches as reliable cost-effective strategies.

CHAPTER 1

INTRODUCTION

1.1 Epidemiology of oral cancer

According to the International Classification of Diseases, 10th revision (ICD-10), oral cancer is defined as malignant neoplasms that occur in the mucosa of the lip, tongue, gum, floor of the mouth, palate, and mouth (World Health Organization, 2015). The malignancy is commonly associated with cultural practices and high-risk habits such as tobacco usage, betel quid chewing, alcohol consumption, and sexual lifestyle (Siegel et al., 2015; Cheong et al., 2017). It predominantly presents as oral squamous cell carcinoma (OSCC) and can arise in either seemingly healthy mucosa or in many cases, is preceded by abnormal lesions (Johnson et al., 2011; Markopoulos, 2012). These abnormalities vary considerably in terms of their clinical presentation, symptoms, and even risks of malignant transformation. While previously labeled as '*precancer'*, World Health Organization (WHO) Collaborating Centre for Oral Cancer standardized these conditions as oral potentially malignant disorders (OPMD) in 2015. The term '*potential*' was used to highlight that not all lesions or conditions will progress into oral cancer (Warnakulasuriya et al., 2020). Some of the conditions that are included under the umbrella term of OPMD are oral leukoplakia, erythroplakia, verrucous leukoplakia, submucous fibrosis, and lichen planus.

In 2020 alone, oral cancer was responsible for around 2.0% of all cancer incidences and 177,757 deaths globally (Sung et al., 2021). Worryingly, the Asian region contributed to more than 65% of the oral cancer incidence and 74% of mortality from the worldwide figures (Wang et al., 2016; Cheong et al., 2017; Sung et al., 2021). Focussing specifically on the Southeast Asian region, the age-standardized rate (ASR) for incidence and mortality were 2.5 in 100,000 and 1.4 in 100,000 compared to the

global ASR of 4.1 in 100,000 and 1.9 in 100,000 respectively (Cheong et al., 2017; Sung et al., 2021). In some of these nations, the high rates were partly contributed by a substantial prevalence of risk factors for oral cancer such as the use of smoked and smokeless tobacco, which in the latter is also combined with another carcinogenic compound- the areca nut. For example, the usage of tobacco among males aged from 15 to 49 exceeds 50% in all Southeast Asia countries, with countries such as Timor-Leste reporting smoking prevalence as high as 96.5% (Ansara et al., 2013; Sreeramareddy et al., 2014). On the other hand, while smoking tobacco among women was comparatively lower, their consumption of tobacco via chewing remained the highest globally (Sreeramareddy et al., 2014; Cheong et al., 2017).

Locally in Malaysia, the ASR was reported to be at 3.0 in 100,000 for incidence and 1.0 in 100,000 for mortality. The incidence rates were more common among males compared to females (Cheong et al., 2017). 742 new cases of oral cancer were detected in 2020, with an estimated 5-year prevalence of 2,199 patients (Sung et al., 2021). Although it was not within the top ten most common cancer here, certain communities such as those of Indian ethnicity as well as the indigenous people of Sabah and Sarawak were identified to be at higher risk due to habits such as betel quid chewing and alcohol consumption (Azizah et al., 2019). Furthermore, oral cancer remained the fourth highest cancer attributed to modifiable risk factors in Malaysia in 2018. The quantification in terms of 'Population Attributable Fraction' at 36.2% reflects the proportion of cases that could have been prevented if the exposure to risk factors were minimized (Teh et al., 2021). Annual national reports also consistently demonstrated a larger proportion of patients presenting at later stages of tumors, attributing to the substantial disease burden (Azizah et al., 2019; Ghani, Ramanathan, et al., 2019).

These numbers are likewise projected to increase leading towards a greater socio-economic implication to both society and healthcare service.

1.2 Financial burden of oral cancer

Management of oral cancer often involves multiple approaches depending on the cancer stage and patient status. These range from simple surgical resections to multimodal treatment involving radiotherapy and chemotherapy. The introduction of newer diagnostic, pharmacological, and treatment technologies coupled with the long-term care of cancer patients contributes to a rapid escalation of cost (Tangka et al., 2010; Warnakulasuriya & Greenspan, 2020). On top of these, Malaysia's public healthcare system also incorporates additional subsidies for the population above the age of 60 years, which forms most of the oral cancer incidences (Kong et al., 2020). Consequently, the bulk of treatment costs will be borne by the Ministry of Health with minimal reimbursement from fee-for-service (World Health Organization, 2012). The recent implementation of the PeKa B40 scheme for the population at the bottom 40% of median household income, which provides financial incentives for transport and the completion of cancer treatment further adds to this existing financial burden (Kong et al., 2020).

Malaysia forms an interesting case for oral cancer management under universal health coverage in an upper-middle-income country. The public healthcare system offers a comprehensive range of health services including cancer treatment, financed mainly through taxation and general revenues from the federal government. While the public health spending consisted of 43.1% of the total national health expenditures, the sector provided about 75.5% of inpatient care and 64.3% of ambulatory care to the population (World Health Organization, 2012; Juni, 2014; Malaysian Ministry of Health, 2019;

Pfister et al., 2020). The fees paid by patients cover both inpatient and outpatient care services, differing by class of accommodation, citizenship, and additional exemptions. However, the charges for Malaysian citizens are heavily subsidized with only 2.6% of expenditures recovered from patient revenues (Malaysian Ministry of Health, 2019). Although the commitments for financial risk protection of its population are exemplary, the increasing disease demands of oral cancer and changing demographics continue to put the public health system under strain (C. W. Ng, 2015).

On the other hand, there is still a lack of information on the financial consequences of treatment among households with oral cancer (Kimman et al., 2015). The available established values from high-income nations are not reflective of the reliance on out-of-pocket (OOP) financing to access preventive and curative care in most of the ASEAN countries. Such unforeseen payments for healthcare, coupled with the debilitating nature of the disease and treatment, can cause households to spiral toward poverty. The ASEAN Costs In Oncology (ACTION) initiative in 2012 reported almost half of the households with cancer patients experienced catastrophic health expenditures (CHE) (Kimman et al., 2015). Patients in advanced stages and socioeconomically disadvantaged were shown to be the most vulnerable. Regardless of the national coverage policies, households were reported to continue to face the devastating financial consequences of cancer.

It was estimated that only less than 2% of the general population in Malaysia incurred OOP payments above 10% of their total consumption due to the high subsidization rates (C. W. Ng et al., 2014). However, the extent of such expenditures in oral cancer and OPMD remains unknown and is expected to be multifold higher. The worrying evidence in oral cancer is that it is more frequent in disadvantaged groups while

simultaneously implicating immense financial distress for treatment, trapping them in an economic crisis (Warnakulasuriya & Greenspan, 2020; Sung et al., 2021). Financial hardship among households may further act as a deterrent for screenings and early interventions, contributing toward later case presentations as seen in Malaysia and many other developing countries (LaBresh, 2016; Malaysian Ministry of Health, 2017). This consequently leads to a greater healthcare burden and more importantly impact their life.

1.3 Impact on quality of life

In addition to high mortality rates, surviving oral cancer patients face a myriad of physical and psychosocial sequelae from both the disease and the intensive treatment regimens. Oral cancer was evidenced to cause one of the highest distress levels among patients, relative to other more common sites such as the breast, colon, and prostate (Carlson et al., 2004). This was partly because the affected regions are critical for the basic function and social interaction of an individual such as breathing, swallowing, and speech (Martino et al., 2008; de Araújo Gomes et al., 2020). Thus treatments such as surgery and radiotherapy, while being vital for the survival of patients, often adversely affect their quality of life (QOL). Furthermore, disfigurement and aesthetic appearances continue to cause anguish and hamper their ability to integrate back into the community, even after a long period of post-treatment (Ojo et al., 2012). Consequently, clinicians and policymakers have been increasingly incorporating health-related quality of life (HRQOL) parameters in their assessments, to understand the patients' journey and plan for a more holistic oral cancer treatment approach.

The HRQOL concept is broadly based on accurate quantifications of the subjective health status of oral cancer through either profile-based or preference-based

instruments. A profile-based approach such as the Head and Neck Functional Assessment of Cancer Therapy (FACT-H&N) for example comprises several domains and aims to describe the various aspects of a patient's health (List et al., 1996). On the other hand, the commonly applied preference-based measure such as the EuroQol 5-dimension scale (EQ-5D), converts generic patient-reported values to a utility index score using country-specific algorithms. The scores usually range between 0 and 1, representing the perceived public's valuation of 'death' to 'perfect health' (Herdman et al., 2011). The utility values obtained can then be further multiplied with the life years of patients to generate outcomes such as quality-adjusted life years (QALY).

FACT-H&N has been validated for the Malaysian population, with studies evidencing the reliability and intuitiveness of the tool in evaluating the HRQOL of oral cancer patients (Doss et al., 2011; Doss et al., 2017). The available reports applying FACT-H&N have evidenced oral cancer greatly impacting HRQOL among patients without treatment and those in later stages. Interestingly, deterioration in certain areas of QOL was observed to persist even after the completion of treatment (Doss et al., 2017). As the socio-demographic data of patient changes and newer technologies and treatment options are introduced, the past established values may not necessarily reflect the current treatment outcomes. Additionally, there is also a lack of evidence on the more important utility values of oral cancer patients in this region (Kularatna et al., 2016). These measures are crucial as they form the basis for cost-utility analysis to guide the assessment of newer health technologies. In the presence of the recently available Malaysian EQ-5D-5L value set, it is also timely to re-evaluate the current HRQOL of oral cancer patients (Shafie et al., 2019).

Investigations into oral cancer patients' experiences should as well include patients with OPMD. This is because these precancerous lesions can also cause a varying degree of discomfort, affects their ability to eat, and more importantly create a fear of disease progressing into malignancies (Kumar et al., 2021). A recent systemic review revealed an overall lack of evaluation on HRQOL of patients with OPMD, especially from Asian countries, which coincidently reported the highest prevalence worldwide (Tadakamadla et al., 2015). Although these precursor lesions are not debilitative, their overarching impact on QOL remains prudent to gauge the willingness of patients to seek treatment or participate in early screening.

1.4 Screening programs and early detection

Oral cancers are often preceded by visible abnormal changes to the mouth. Such changes can be detected easily by a visual oral examination that does not involve surgically invasive procedures or expensive imaging technologies. Numerous studies have consistently reflected the feasibility, accuracy, and positive predictive values of such oral examination (Brocklehurst et al., 2013). Once identified, close monitoring, risk-habit minimization counseling, and active interventions such as the removal of lesions can mitigate the risk of progression into malignancy. It is important to highlight that screening tests are not intended as diagnostic tools but to detect premalignant changes and early malignancies so that successful treatment can be implemented. In the case of oral cancer, as illustrated in Figure 1.1, the higher effectiveness of early-stage treatment can be translated to an increase in survival and correspondingly patients' QOL.

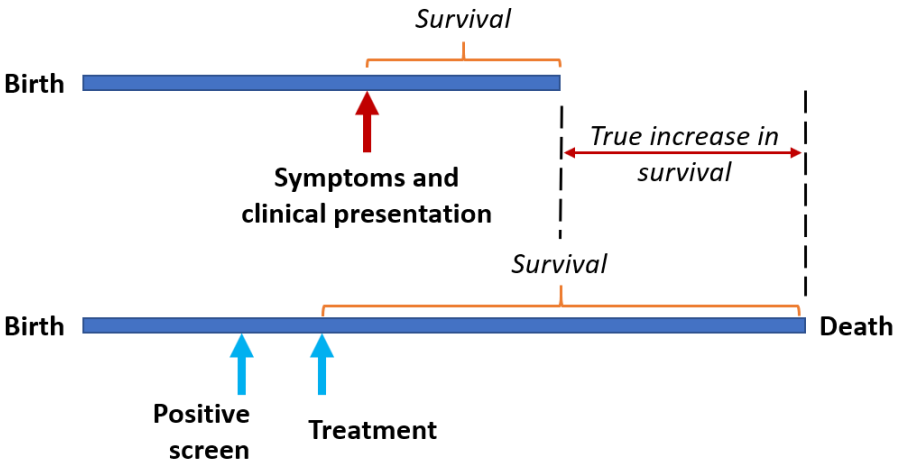

Figure 1.1 Illustration of an effective screening program

Screening for oral cancer, especially at a population level, is yet to be advocated due to inadequate evidence to justify the efforts and expenses (Petersen, 2009; Moyer, 2014; Brocklehurst et al., 2018). Currently, out of the ten principles of a successful screening program established by Wilson et al. (1968) as shown in Table 1.1, only the first principle is realized. Evidence of the rest of the key principles is either inconclusive or lacking (Warnakulasuriya & Greenspan, 2020). Nevertheless, many studies and evaluations have been conducted to assess the viability of targeted screening in high-risk populations and those seeking professional health care (Speight et al., 2006; Kumdee et al., 2018; Thankappan et al., 2020). The recent paradigm shift in the delivery of healthcare via the application of telemedicine and mobile phones has created new opportunities for fulfilling the principles of the screening program, especially in terms of cost-effectiveness and acceptance by the population (Birur et al., 2015; Warnakulasuriya & Greenspan, 2020).

Table 1.1 Wilson and Jungner's ten underlying principles for the design of a screening program

1	The condition to be screened for should be an important health problem	6	The test should be acceptable to the population
2	There should be an accepted and effective treatment for patients with recognized disease	7	The natural history of the condition, including the development from latent to declared disease, should be adequately understood
3	Facilities for diagnosis and treatment of those screened positive should be available	8	There should be an agreed policy on who should be offered treatment and the appropriate treatment to be offered
4	The disease should have a recognizable latent or early symptomatic stage	9	The program should be cost-effective
5	There should be a suitable test or examination	10	Screening should be a continuing process and not a "once and for all"

Adapted from Wilson et al. (1968)

Early detection of OPMD and oral cancer coincidently forms the major component of cancer control programs in Malaysia (World Health Organization, 2002). The Ministry of Health adopted the health goal of ensuring at least "30% of oral cancer cases are detected at stage I" as part of its National Oral Health Plan (Malaysian Ministry of Health, 2011). This was aimed to be achieved by strengthening and expanding the screening capacity in public healthcare. Under the current status-quo, oral cancer patients are screened either via self-referral to primary care facilities or through community screening camps. Both approaches aim to detect lesions earlier and effectively be referred for treatment in tertiary care centers. These programs also include awareness campaigns to encourage the public to participate in screening and health professional training to recognize early signs and symptoms of the disease.

The community screenings camps are based on targeted, high-risk populations in villages, estates, or rural areas. Such communities are identified and healthcare teams are mobilized to conduct screenings and oral examinations. This often involves extensive human resources and face logistical challenges to transport the team of

specialists to remote areas. While the initiative vastly improves access to care in these largely isolated communities, the numbers of positive referrals are relatively trivial. In 2018 for example, out of 2,945 individuals screened via community screening, only five referrals to oral surgeons were made. The annual number of referrals ranged from zero to 50 over the past 11 years (Malaysian Ministry of Health, 2018).

The main point of care for screening in Malaysia remains from the walk-in patients to primary clinics. They can either be from self-referral upon discovery of suspicious lesions or opportunistically identified by healthcare professionals during their routine care. From 2014 to 2018, a total of 425,843 individuals were screened, with 1,491 referred for further examinations (Malaysian Ministry of Health, 2018). Furthermore, a higher number of malignant cases were detected among patients screened in dental clinics compared to community screening camps. This reflected the significant role dentists in primary care play in oral cancer screenings.

However, almost after a decade of implementation of various initiatives, the national goal is yet to be realized due to numerous sociodemographic factors and challenges to the operation of strategies (Malaysian Ministry of Health, 2018). Based on the local cancer registry data from 2012 to 2016, only 15.6% of all oral cancer cases recorded were in stage I (Azizah et al., 2019). Most diagnoses were consistently still being made at stage IV. These echoed similar findings around the world, with more than 60% of patients regularly presenting with later stages of the disease (Brocklehurst et al., 2013; Walsh et al., 2013). Such a trend leads to a significantly elevated risk of morbidity and mortality from locoregional recurrence and distant metastasis (Rusthoven et al., 2010; Walsh et al., 2013; Huang et al., 2019).

These delays were primarily related to patient awareness and knowledge level, especially in at-risk populations. Additionally, logistic and financial barriers to access dental services by ethnic minorities and populations in rural areas were also identified as possible factors (Noonan, 2014). Furthermore, a lack of experience and vigilance by the primary healthcare personnel in detecting early signs and symptoms of oral cancer can further compound such diagnostic delays (Gajendra et al., 2006; Monteiro et al., 2012). Thus there is a dire need for transformation of the current conduct and approach to oral cancer screening to safeguard the public and reduce the healthcare burden.

1.5 Application of teledentistry

"Telemedicine" is the term used to describe the application of information and communication technologies to deliver healthcare across areas. In dentistry, this involves the exchange of clinical data and images for diagnosis, screening, consultations, treatment, and planning (Jampani et al., 2011). Its use is of utmost value especially during this pandemic, besides in rural areas and settings which lack the presence of specialists. Consultations via teledentistry can be conducted in 'real time' or using the 'store and forward method', with the latter involving an exchange of clinical and static documentation collected by dental practitioners (Figure 1.2). For dental use, store and forward technology offer exceptional outcomes without being affected by connectivity or high operational cost. Typically, the system consists of a computer, a digital camera, and an internet connection (Jampani et al., 2011). In recent years, the processing ability combined with the necessary hardware of mobile phones has also enabled it to be an effective tool, giving rise to Mobile Phone Imaging Teledentistry (MPIT).

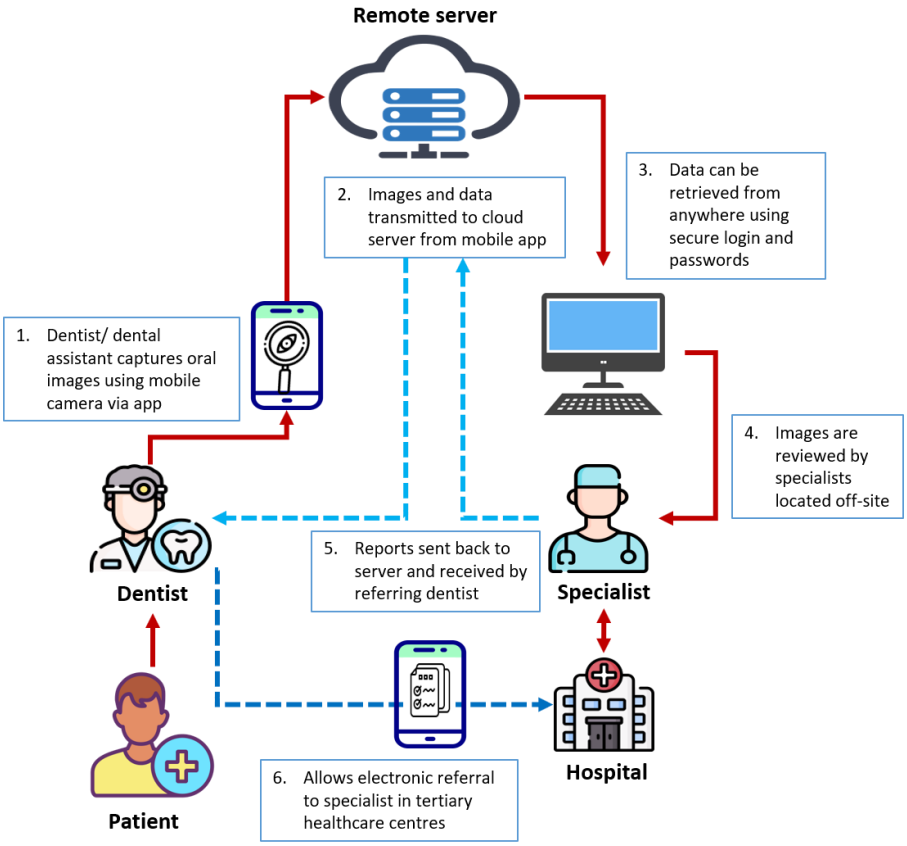

Figure 1.2 Cloud-based store-and-forward telemedicine app

In Malaysia, a novel application called MeMoSA® (Mobile Mouth Screening Anywhere) was developed by Cancer Research Malaysia (CRM) to address the key challenges of early detection of oral cancer (Haron et al., 2020). The MPIT application serves as a secured platform for communication between primary healthcare practitioners and specialists located off-site. It also allows easy documentation of oral lesions through photography to improve diagnostic and referral accuracy. The application is intended for a licensed primary healthcare provider or a healthcare specialist with an active annual practicing certificate. Users are allowed to chat, contribute, participate and transmit content upon written consent from each identifiable individual involved. Registered clinicians enter patients' details such as

risk habits, sociodemographic information, and nature of lesions in addition to capturing the images of the mouth using a mobile phone camera operated via the app.

The data will be uploaded to a secured private server using a cellular data network instantaneously or saved offline and uploaded automatically upon the availability of the internet. Oral specialists would then be able to log in to a customized website to access the information and provide the necessary feedback. In addition, it also has a patient tracking system to enable robust monitoring and follow-up of patients (Haron et al., 2020). Data privacy and security are safeguarded by CRM in accordance with Personal Data Protection Act 2010. Based on the Medical Device Authority of Malaysia, the MeMoSA® application is not categorized as a medical device as it only functions to facilitate communications and coordination in patient management.

MeMoSA® was initially field-tested at a routine community screening in a rural setting in West Malaysia. All dentists that participated in the program agreed with the ability of the application to facilitate early detection of oral cancer and assisted in lesion identification through communication with specialists (Haron et al., 2020). It was further evaluated prospectively for referral accuracy and concordance with conventional clinical oral examinations (COE). The evaluation and recommendations of lesions remotely by specialists via MeMoSA® showed a sensitivity of more than 80% for detecting a lesion, an accuracy of 87% for categorizing the type of lesion, and 85% concordance with patient referral decisions when compared with COE by specialists at the site (Haron et al., 2021). Such findings were consistent with Birur et al. (2015) in a similar study exploring the impact of MPIT on oral cancer surveillance by health care workers in India. The study evidenced that MPIT was effective to enable non-specialists with minimal training to refer high-risk lesions. This was achieved via

the ability to communicate medical information with specialists located off-site. Such initiatives can significantly improve the pace, efficiency, and detection of oral cancer (Bradley et al., 2010).

1.6 Cost-effectiveness of MPIT

Numerous consensus has been formulated to incorporate MeMoSA® as a valuable detection tool. Its implementation can be varied based on coverage, target population, screening methods, and test performances. The increasing choices create a dilemma in seeking and recommending the best alternative. However, the most critical factor in preventing the institutionalization of such strategies are uncertainties surrounding their cost-effectiveness (Brocklehurst & Speight, 2018). This is even more critical in Malaysia as both the preventive measures and treatments for oral cancer and OPMD are financed by MOH. Any implementation of new additional initiatives should be evaluated against the overall cost-saving and value-addition to services provided.

'Economic evaluation' is thus needed to appraise and optimize health outcomes in a limited resource setting. It is defined as the comparative analysis of alternatives in terms of both their costs and consequences (Drummond et al., 2015). The cost components are always measured in terms of monetary units based on the perspective taken for the calculation and the extent of expenditure included. For example, a societal cost perspective takes into consideration of all cost elements- expenditures for the provision of healthcare services, patient spending, and other expenses to the society. This often encompasses 'direct costs' which are related to service provision and utilization, in addition to 'indirect costs' from productivity losses to the society due to time off work as a result of illness and treatment (Drummond et al., 2015; Babar, 2016).

On the other hand, the consequences or outcomes of the strategies evaluated can be measured in various ways and determine the type of evaluation that is conducted. There are four main types of evaluation commonly used in healthcare- (1) cost-minimization analysis (CMA), where outcomes are assumed to be equal and only cost components are compared; (2) cost-effectiveness analysis (CEA), where outcomes are in natural or physical units; (3) cost-utility analysis (CUA), where a generic measure such as QALY is used and (4) cost-benefit analysis (CBA), where the benefits are expressed in monetary terms. While the objective of each study ultimately determines the type of analysis selected, recent guidelines and health technology agencies recommend the use of CUA for decision making due to ease of interpretation and comparison across the horizon of different service provisions (Table 1.2) (Drummond et al., 2015; Donna Rowen et al., 2017). Furthermore, the application of QALYs is considered apt in oral cancer specifically as it can reflect the health benefits of early detection in terms of both quantity and quality of life. Thus, ideally, decisions should be substantiated by calculating the incremental cost-effectiveness ratio (ICER), which expresses the cost per QALY gained for the introduction of newer strategies.

Previous economic studies on telemedicine have shown that careful evaluation of its cost-effectiveness is required to ensure worthwhile investment in the technology (de la Torre-Díez et al., 2015). Even though most of the research has concluded that telemedicine is cost-effective in improving patient health outcomes, some studies have reported the contrary and that it does not follow the standard evaluation techniques (Whitten et al., 2002; N. Aoki et al., 2004; Bergmo, 2009; Hema, 2011; Zurovac et al., 2012). Among the main limitations of these evaluations were smaller sample sizes, lack of randomized controlled trials (RCT), and methodological flaws. Most studies were also focused on the cost-saving of these initiatives while disregarding potential

health benefits for patients (Bergmo, 2009). This underscores the need to evaluate the cost-effectiveness of each novel intervention as early detection of oral cancer may impact both the QALYs and the long-term societal financial burden.

Table 1.2 Country-specific economic evaluation recommendations

Country	Producing body	Year	Preferred economic evaluation	Recommended perspective
Malaysia	Ministry of Health, Malaysia	2019	CEA or CUA	Healthcare provider
Thailand	Health Intervention and Technology Assessment Program	2008	CUA	Societal
Taiwan	Taiwan Society for Pharmacoeconomic and Outcomes Research	2006	No specific recommendation	Societal
United States of America	Academy of Managed Care Pharmacy	2016	CUA	Payer
United Kingdom: Scotland	Scottish Medicines Consortium	2016	CUA	Healthcare provider
United Kingdom: England and Wales	National Institute for Health and Care Excellence	2013	CUA	Healthcare provider
Australia	Pharmaceutical Benefits Advisory Committee	2016	No specific recommendation	Healthcare provider
Germany	German national institute for quality and efficiency in health care	2009	CEA or CUA	Healthcare provider
Spain	Catalan Department of Health	2014	CUA	Healthcare provider

1.7 Study significance and problem statement

Based on the current trend of prevalence and performance of screening programs in Malaysia, the incorporation of MPIT such as MeMoSA® may be much needed to reduce the societal burden of oral cancer. This is because well-distributed trained specialists are needed to identify high-risk lesions and malignancies at earlier stages. Unfortunately, specialists care is not readily available, particularly in rural and geographically remote areas. For example, the public dental clinic-to-population ratio was 1:89,000 in Sabah, with the national average remaining at 1:38,000 (Bohari et al., 2019). Furthermore, as of 2018, there were only 284 clinical dental specialists and 85 dental public health specialists in the public healthcare sector (Malaysian Ministry of Health, 2018). These numbers remain insufficient for oral cancer screenings to be conducted in person, especially in an already congested tertiary care setting. Therefore if no drastic measures are taken, the disease burden of oral cancer will continue to take its toll on the healthcare budget and also the society.

While screening performances can be assessed at ease, the implications of such initiatives over the course of the disease remain unknown. Designing and conducting clinical trials to explore these strategies are often hampered by the time and cost burden. In recent times, the development of economic modeling in cancer provided a mechanism to address this limitation. Several models, albeit varying in their design and approach have managed to answer the question of whether these interventions are cost-effective in their setting (Van der Meij et al., 2002; Speight et al., 2006; Dedhia et al., 2011; Kumdee et al., 2018).

Both cost-effectiveness analysis and decision analysis are systematic approaches to support decision-making by policymakers and physicians. It can facilitate current

decisions on the implementation of MeMoSA® under complex and uncertain scenarios. Compared with observational and controlled trials, these mathematical tools allow for a robust investigation of oral cancer screening strategies with much ease and within limited resources (Ryder et al., 2009). Thus, this study aims to provide evidence-based analyses on the cost-effectiveness of MPIT application, for screening and managing patients with oral lesions compared to the COE.

1.8 Research question

Based on the hypothesis of early detection of oral cancer by using MPIT would lead to early diagnosis, down-staging of the disease, and prevention of oral cancer-related death, this study aims to answer three main questions:

I. What are the societal cost of MPIT and conventional oral cancer screening in Malaysia?

II. Is the implementation of MPIT cost-effective in a Malaysian public healthcare setting?

III. What is the break-even cost for the implementation of MPIT?

CHAPTER 2

LITERATURE REVIEW

2.1 Economic evaluation and modeling

Randomised controlled trial (RCT) is considered the gold standard for assessing the cost and benefits of any healthcare intervention. This is because reliable information in real-world situations can be garnered with minimum assumptions. However, the incorporation of RCT in the evaluation of cancer screening programs is limited by several pertinent factors. Primarily, the pathophysiology of oral cancer and the latency of OPMD causes the study period to be extremely time-consuming and expensive. In addition, trial-based evaluations are also limited by the choice of comparators and scenarios that can be explored (Petrou, 2012). In such scenarios, alternative designs such as modeling studies are seen to be more pragmatic and feasible in terms of the resources required. Due to this, in recent years modeling approaches are being favored to assess the cost-effectiveness of numerous cancer screening programs (Brocklehurst et al., 2013).

A decision-analytic modeling study involves the synthesis of data from the literature to develop mathematical or statistical frameworks to generate outcomes and consequences. The approach helps decision-makers to understand the relationship between the effectiveness and costs of alternative strategies while illustrating the uncertainties around such decisions. Various types of models are available, each differing in terms of complexity and predictive accuracy. For example, a cohort Markov model is more suited for a sequence of events that occurs over a period of time. Due to that, many cancer studies have opted for Markov modeling to simulate disease and the effect of screening on oral cancer (Speight et al., 2006; Dedhia et al., 2011; Kumdee et al., 2018). On the other hand, some investigators chose to trade the

more accurate but complex Markov model with a more straightforward decision tree. Regardless of the preference, it is critical for the types of model to be evaluated alongside other approaches as a guide for both researchers and policymakers.

2.2 Search strategy and conduct

A systematic search of studies on economic evaluations of oral cancer screening was carried out on four major databases – Medline, CINAHL, Cochrane, and PUBMED, two health technology assessment databases- Centre for Reviews and Dissemination of the University of York and The International Network of Agencies for Health Technology Assessment (INAHTA) and EBSCO open Dissertations for relevant theses. The search strategy was based on the following criteria in Table 2.1 and was confined to publications from January 1, 2000, till December 31, 2018. This time frame was chosen to ensure the outcomes measured were reflective of the current risk factors and treatment advancements.

Table 2.1 Search strategies for studies

PICO	**Criteria**
Population	Adult patients, with oral cancer or OPMD
Intervention	Oral screening programs, irrespective of the method Carried out in any setting Any form of recruitment method
Control	No screening / conventional methods
Outcomes	Contains economic evaluations

A Cochrane review of Appropriate Medical Subject Headings (MeSH), thesauruses, and specific keywords were combined using Boolean operators. Examples of search terms are attached in APPENDIX A. For papers subsequently selected for full-text screening, the bibliographical reference lists were also hand searched for other relevant

studies. Papers were not confined to the English language. However, efforts were carried out to obtain a copy in English for abstraction and quality assessment.

Titles and abstracts were first scrutinized by a reviewer based on relevance. The full text of selected studies was later obtained and reviewed independently by two reviewers. There were no restrictions in terms of the population characteristics, patient recruitment methods, study design, and implementation of strategies to ensure a comprehensive review. Studies were only excluded if (1) full text was unavailable; (2) has no or is partial economic evaluation; (3) screening consisted of other than visual oral examinations, and (4) not an original article. At this stage, excluded studies were listed and the reason for exclusion was reported. Any discrepancy in the selection of papers was discussed between the reviewers till a mutual agreement was reached.

Numerous checklists are available to assess the risk of bias in economic evaluation studies. The simple Quality of Health Economic Studies (QHES) instrument was first used by both reviewers to rank studies according to their quality scores. The list consists of 16 items with varying weightage based on the importance of each criterion (Ofman et al., 2003). Following the recommendations from the Cochrane collaboration and the National Institute for Health and Care Excellence (NICE), reviewers also applied the Philips checklist to assess the quality of the identified modeling studies (Philips et al., 2006; Wijnen et al., 2016). The checklist consisted of 32 relevant questions to guide and critically assess decision-analytic modeling (Meadows et al., 2013).

Data were extracted into three major sections to aid discussions: (1) study characteristics, (2) reported outcomes, and (3) model design. A standardized data extraction form was developed in Microsoft Excel based on literature and expert

review. Extracted information was summarised into evidence tables based on the set sections. The data were extracted by both reviewers and counter-referenced for completeness and accuracy. To allow for a meaningful comparison of ICER values, studies published in United States dollars (USD) were adjusted to the 2018 value using the Consumer Price Index (CPI). For studies conducted in other currencies, the values were adjusted to 2018 using the CPI followed by conversion to USD using the Purchase Power Parity. This was done to consider each nation's economic productivity and living standards. All of the conclusions and outcomes were also analyzed qualitatively for variabilities to guide the conduct and design of future studies.

2.3 Search results

The initial literature search yielded 362 papers. After the removal of duplicates and irrelevant studies, the remaining 28 studies were accessed for eligibility. Finally, six studies, four of which adopted the modeling approach, were included in the final review and discussion (see Figure 2.1). The rationale for study exclusion is reported in APPENDIX B. Overall the number of studies on the cost-effectiveness of screening programs for oral cancer was rather small compared to other types such as prostate and breast cancer (Schiller-Frühwirth et al., 2017; Sanghera et al., 2018). This shows that even though numerous screening programs for oral cancer are recommended and implemented at various levels, these programs are often not evaluated rigorously in terms of economic benefits.

It was difficult to assess the studies identified based on a single quality assessment tool as they differ extensively in terms of design. Based on the more general QHES list, five of the studies were considered excellent with scores above 90, while the study by Van der Meij et al. (2002), was arbitrarily assigned to be moderate (APPENDIX C).

The most frequent criteria (n=3) that were commonly not fulfilled were the analytic time horizon and discounting rate of benefits and outcomes. The lower score for Van der Meij et al. (2002) was partly due to the input parameters primarily being based on estimates which were not described. This reduces the score of criteria such as methodology for data abstraction, quality of the source, besides appropriateness of cost measurement and estimates.

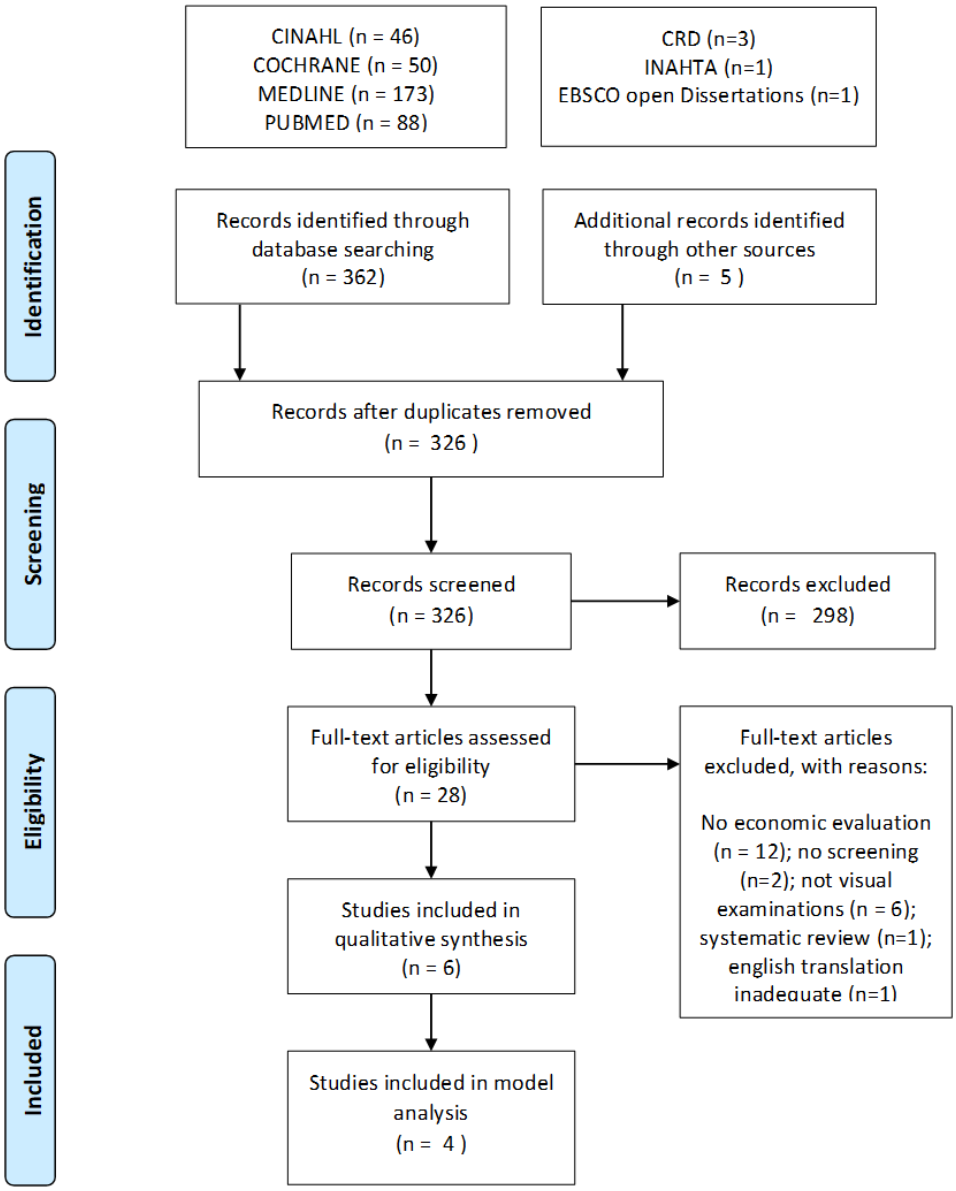

Figure 2.1 Flow chart of literature search