EARLY HEALTH ECONOMIC EVALUATION OF MEDICAL DEVICES

EARLY HEALTH ECONOMIC EVALUATION OF A NOVEL MEDICAL DEVICE AND THE DEVELOPMENT OF A CONCEPTUAL GUIDING FRAMEWORK

By

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Early Health Economic Evaluation of a Novel Medical Device and the Development of a Conceptual Guiding Framework

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ABSTRACT

Background and objectives

To avoid unsuccessful implementation of new health technologies in clinical practice, it is important to investigate their potential cost-effectiveness before adoption, using the health technology assessment (HTA) process. Cost-effectiveness analysis (CEA) techniques tailored for the early stages of a health technology when there is limited evidence available, may guide more efficient resource investment in the development process, such as conducting additional studies that would inform key parameters to strengthen the economic model. However, knowledge and application of early CEA has been limited. A key challenge is trying to conceptualize an economic model with limited information regarding a product's exact use in clinical practice, and how to use the existing limited data as input parameters for the model.

In this thesis, early CEA refers to the premarket stage of a product's lifecycle. The objective of this thesis was to develop a guiding framework for conducting early-CEA for medical devices with limited evidence, by contextualizing all of the available methods in the literature, in order to help support conducting early-CEA and to increase its usefulness.

Methods

Project 1: A systematic review was conducted with the purpose of identifying and critically appraising all of the available methods for conducting early-CEA for medical devices with limited evidence, and to propose a conceptual guiding framework to conduct robust early-CEA.

Project 2: Appropriate methods identified in the systematic literature review from project 1 were applied to conduct an early-CEA of *Straticyte*^{TM}, a novel prognostic tool, when used in combination with the current standard of care (SOC), histopathology, for diagnosing oral potential malignant or pre-malignant lesions (OPLs) in adults aged 35 years or older from a private and patients' perspective.

Project 3: The lifetime costs, patients' outcomes, and cost effectiveness of *Straticyte*^{TM} in combination of histopathology compared to histopathology alone among oral cancer patients were assessed in an economic evaluation from the public payer perspective, by using the output from project 2 as a starting point.

Results

Project 1: Thirteen methods from 26 studies were identified and grouped based on their purpose in conducting CEAs with limited evidence. Based on these methods, a step-wise conceptual guiding framework of how to conduct CEA for medical devices with limited evidence was created, where the methods were introduced at each step based on their general aim for conducting CEA.

Project 2: The early-CEA demonstrated a high probability that *Straticyte*^{TM} and histopathology will be cost-effective for the detection of OPLs, which in turn encourages continued investment by manufacturers into the product, and suggests that future investment by the healthcare system and individual patients may be worthwhile.

Project 3: The long-term economic evaluation demonstrated potential beneficial downstream effects to the healthcare system from introducing *Straticyte*^{TM} to current

clinical practice; due to fewer cancer cases requiring treatment over the long-term. This highlighted the considerable cost savings to the public healthcare system, if payers invest in a preventative technology in dentistry that could have downstream effects on publically funded cancer care.

Conclusions

The conceptual guiding framework of early-CEA of medical devices with limited evidence that was developed in this thesis classified and harmonized the available methods to support the utilization of early-CEA for key stakeholders in medical device development, and implementation. The premarket assessment of *Straticyte*^{TM} demonstrated the high probability of it being cost-effective, which may encourage investment for manufacturers, and for public payers, in this health technology. The long-term CEA demonstrated the potential positive downstream impact of *Straticyte*^{TM} on the healthcare system as a result of its adoption in the market. Further, given that *Straticyte*^{TM} is developed for use in dentistry, a privately funded healthcare service, this thesis highlights the advantage of public payers' investment in preventive health technologies in dentistry that have downstream effects in the publically funded medical healthcare system.

PREFACE

This thesis is a "sandwich thesis" consisting of three individual projects prepared for publication in peer-reviewed journals. One of the chapters is published and the two others are submitted to peer reviewed journals and are under review. The contributions of Shoghag Khoudigian-Sinani to all of the papers in this thesis include: developing the research ideas and research questions, collecting the required data, performing the analyses, interpreting the results, preparing the manuscripts, submitting the manuscripts for publication, and responding to reviewers' comments. The work in this thesis was conducted between Spring 2014 and Spring 2018.

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The work represented herein would have not been possible without the constant support of many amazing individuals. They did not only encourage and guide me through a turbulent but exciting journey, but they also made sure to celebrate all my achievements.

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Last but not least, I would like to thank my immensely supportive family. There are no words to convey how much I appreciate their love and constant support. To my husband, thank you for believing in me and inspiring me to do my best every single day of this challenging but amazing journey. To my family, thank you for showing me unconditional love, taking care of me, teaching me determination and perseverance, generously giving your time and energy to raise me, and making me the person I am today.

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LIST OF SUPPLEMENTARY MATERIALS

LIST OF ABBREVIATIONS

AHP	Analytic Hierarchy Process
APCOI	Application, Population, Comparator, Outcome, Intervention
CAD	Canadian
CCO	Cancer Care Ontario
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CPI	Consumer Price Index
EEs	Economic Evaluations
HCPs	Healthcare Professionals
HCRU	Healthcare Resource Utilization
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICES	Institute for Clinical and Evaluation Sciences
ICUR	Incremental Cost Utility Ratio
MC	Monte Carlo
MT	Malignant Transformation
MTR	Malignant Transformation Rate
NMB	Net Monetary Benefit
NPV	Negative Predicted Value
O&M	Oral and Maxillofacial
OCR	Ontario Cancer Registry
OPLs	Oral Potential Malignant or Pre-Malignant Lesions
OWSA	One-Way Sensitivity Analysis

PICO	Population, Intervention, Comparator, Outcome
PPV	Positive Predicted Value
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	Research and Development
RR	Relative Risk
SOC	Standard of Care
VOI	Value of Information
WTP	Willingness to Pay

CHAPTER 1 - Thesis Introduction

Cost-Effectiveness Analysis (CEA) in Health Technology Assessment (HTA)

There are increasingly more innovations in healthcare technology, and limited healthcare resources. Health technology assessment (HTA) is a multidisciplinary process that is used to help make informed decisions about resource allocation for new technologies, including pharmaceuticals and medical devices (1; 2). HTA encompasses clinical effectiveness, cost-effectiveness, and the ethical, legal, and social implications of health technologies on patient health and the health care system (1; 3). Given the limited healthcare budgets, economic evaluations (EEs) are emphasized, and, as a result, cost-effectiveness analyses (CEA) are increasingly being used to determine value for money for health technologies (4; 5). CEAs allow for the assessment of the gain in health relative to the cost of different health technologies (4; 5). If a technology is deemed sufficiently beneficial to patient health relative to its cost, it has a higher likelihood of being reimbursed. Reimbursement increases the product's adoption within the healthcare system, and leads to improved patient health and a return on investment for manufacturers (6; 13).

There are established methods and guidelines for conducting EEs, however, these guidelines pertain primarily to pharmaceuticals, and have not been as successfully applied for medical devices (7). EEs for pharmaceuticals differ than those for medical devices, most notably because the regulatory framework for medical devices requires less clinical evidence than pharmaceuticals before they are approved for the market and therefore there is little information available to demonstrate efficacy (7; 8). In addition, medical devices are continuously being updated and thus any evidence that has been collected is often out of date by the time an HTA is to be conducted (9). CEAs are mainly conducted when health technologies are ready to be introduced into the

market, after substantial investment in the development of the product (10). However, over the last few decades, there has been increasing interest in conducting CEAs at earlier stages, which encompasses basic research, translational research, and clinical research (10; 11). Commonly, early CEA is done at premarket stages, when some clinical research has been conducted but the evidence is limited, which is the focus of this thesis. This has become an attractive approach for manufacturers because it can be used to make more informed decisions related to further product development, barriers and facilitators to coverage and reimbursement, and pricing strategies for the health technology, with the goal of investing more efficiently to increase the likelihood of reimbursement (10; 12; 13).

Early-CEA for Medical Devices with Limited Evidence

Conducting CEAs for a new health technology at its premarket stage when there is limited evidence provides insights into its potential cost-effectiveness, thus informing decisions on its commercial viability (10; 14). This allows to either stop further investment if the product is unlikely to be successful in the healthcare system, or to help identify gaps in knowledge to inform more efficient investment in its success (15; 20). Methodological advances in early-CEA have been explored, with the majority of the literature related to pharmaceuticals with substantial commercial value (10). Early-CEAs are less commonly conducted for medical devices, despite the fact that many years and resources are spent on research and development (R&D) of new medical devices that ultimately fail to gain adoption (16). However, there has been an increase in early-CEA studies evaluating medical devices since 2006 (17). The expansion of the literature has been fueled by high R&D costs, shorter life spans of medical devices compared to pharmaceuticals as well as payers need for evidence-informed decisions about reimbursement (8; 16).

Benefits of Conducting Early-CEA with Limited Evidence for Medical Devices

Early-CEA can deliver valuable information on the potential value and impact of a medical device with limited evidence. In general, depending on how early the medical device is assessed and the extent of the evidence, early-CEA can support manufacturers with strategic R&D decision making, go/ no-go decisions to identify potentially successful medical devices, and assessment of future reimbursement and pricing (13; 18).

More efficient decisions regarding product development can streamline innovations by making earlier decisions to invest in further pursuing a technology or redistribute resources to another, more promising technology, which benefits the healthcare landscape overall (5, 8; 10; 12; 13; 19). In addition, early-CEA can provide insights about how the device will potentially be used in clinical practice by understanding the needs of end users, including key opinion leaders and healthcare professionals (8). By disseminating clinical and economic information early in the product's lifecycle, could help determine whether there are potential barriers to implementation, such as training required to use the technology. Early-CEA can also clarify where the device will fit in the healthcare system, thus who will potentially fund it (7; 8).

Furthermore, decision makers would know about upcoming innovations, their characteristics, as well as have preliminary evidence of the consequences of their adoption. It would allow decision makers to incorporate the value and economic properties of an innovation in their current decision-making, forecasting and anticipation of future technological development (21). With new emerging technology in mind, decision makers would have greater ability to efficiently allocate resources and optimize budgeting. Thus, stakeholder input from end users and HTA practitioners

can lead to more efficient investment of resources when creating and synthesising the necessary evidence to strengthen the device's profile, widening its potential usage, and expediting the process of market adoption (5; 12; 13).

Early-CEA would also help identify potential barriers and facilitators for greater market access and appropriate pricing. This impacts the steering of the new health technology's diffusion, adoption, and potential success in the healthcare system (21). Despite the utility of early-CEA for medical devices, it is not the current standard practice among manufacturers, because the characteristics associated with medical devices make them more challenging to assess compared pharmaceuticals (22; 23).

Challenges of Conducting Early-CEA with Limited Evidence for Medical Devices

There are a number of challenges for conducting early-CEA for medical devices with limited evidence including: (1) the product's optimal position(s) in the clinical pathway is (are) unclear, (2) there is limited clinical effectiveness evidence, (3) there are limited available published methodologies, (4) there is no consensus framework on best practice methodologies, and (5) given the lack of methodological standards, there is no centralized database of available medical devices for healthcare practitioners and policy decision-makers, which limits how reliable market research is to inform early CEA models.

First, the most important factor influencing the limited uptake of early-CEA is the insufficient available data, and the imprecision of existing data, which may result in uncertain and inconclusive economic evidence (24). Second, its full potential use and benefit in different scenarios is unknown, and long-term outcomes are difficult to estimate, thus identifying and defining the target

patient group (i.e. indication of the medical device) is challenging (7; 8). Therefore, defining the scope of early CEA with limited evidence using existing methodologies available in EE guidelines for conducting classic CEA is not readily applicable (8). Third, even with the data available, there are methodological weaknesses in using it, and no consensus framework to conduct early-CEA with limited evidence. Early-CEA models are advised to promote uniformity and transparency, enabling the comparison of results for different technologies, and to critically appraise the methodological quality of the evaluation and to ensure potential issues are appropriately handled (24). Lastly, eliciting expert's opinion for primary market research to inform early CEA models would have limited usefulness, because few health care professionals will be aware of the scope of medical devices available to them, and how they may use the new device given the limited evidence on its effectiveness (7; 8).

Need for a Guiding Framework for Conducting Early-CEA with Limited Evidence for Medical Devices

A guiding framework for early-CEA with limited evidence would help manufacturers, decision makers, HTA assessors, healthcare providers (HCPs), and ultimately patients (21).

Conducting early-CEA using a pre-specified framework would assist manufacturers to systematically identify and apply appropriate methods. This in turn can help manufacturers develop better evidence that is more likely to be accepted by HTA practitioners, healthcare providers and patients (21). A standardized framework for guiding early CEA may incentivize industry to increase uptake of conducting them, and improve innovation. With a guiding framework, HTA practitioners apply and improve the existing methodology, and help increase the validity and feasibility of early CEA with limited evidence (21). Further, standardized methods

could allow HTA advisors to create registries of assessed medical devices, and could then be used to support further research.

Thesis Objectives

The rationale for this thesis is twofold: 1) to determine the short- and long-term cost-effectiveness of a novel health technology prior to market launch; and, 2) to create a guiding framework for conducting early CEA with limited evidence for medical devices within HTA. The aim is to identify, harmonize and standardize the methods of economic evaluation, particularly with early-stage data, in order to facilitate its use, as well as enhance transparency and comparability among medical devices. The anticipated impact of this guiding framework is to promote the development and widening use of trustworthy early-CEAs with limited evidence in HTA for medical devices. This will ultimately result in more comprehensive guidelines for conducting early-CEA with limited evidence for medical devices, which are of great interest for key stakeholders. In general, this comprehensive guideline will help guide and eventually impact the steering and diffusion, adoption and the use of new health technologies, mainly through coverage and reimbursement. This becomes of great importance among manufacturers given the short life cycles of medical devices.

The more specific objectives, which were formulated to guide different phases of this research, are described in the relevant chapters in this thesis report.

Overview of Thesis Chapters

This thesis was conducted in multiple phases, and the overall structure of the thesis is illustrated in Figure 1. This thesis consists of three manuscripts. One manuscript (Chapter 3) has already been

published in a peer-reviewed journal, and the other two manuscripts (Chapter 2 & 4) are currently under peer-review in well-respected peer-reviewed journals.

Chapter 1: This chapter serves as the background to the thesis, as it provides some basic information about conducting CEAs in HTA, followed by how early-CEA with limited evidence plays a key role for medical devices. It also talks about the benefits and challenges of conducting early-CEA with limited evidence in HTA and highlights the need for a guiding framework for conducting early-CEA with limited evidence for medical devices.

The challenges described in this introductory chapter also allows to frame the research problem, further outline the justification for this research, introduce the study objectives, and link the thesis chapters.

Chapter 2: This chapter provides an overview of the current state of early-CEA with limited evidence for medical devices. Describes and critically appraises all of the available methods used during different stages of conducting CEA with limited evidence by identifying them through a systemic review of the published literature. The focus of this chapter is on methods used to collect, synthesis evidence as well as conduct early-CEA with limited evidence for medical devices. This review identifies and classifies the methods proposed and applied in the literature, which in turn is used to build a guiding framework on early-CEA for medical devices with limited evidence. The robust early-CEA with limited evidence would provide useful insights into the potential value of the product at the moment of analysis and to meet the requirements of fully developed models at later stages of the products life cycle by easily integrating insights and evidence that arise. The chapter is under peer-review process in the International Journal of Technology Assessment in Health Care (IJTAHC).

Chapter 3: This chapter applies the appropriate methods identified in the systematic literature review to estimate the cost-effectiveness of the introduction of a new prognostic tool, *Straticyte*^{TM}, to the SOC for the detection of OLPs from the private and patients' perspectives. This analysis is done when *Straticyte*^{TM} is at premarket stage with very limited evidence on (1) its optimal position(s) in the clinical pathway, (2) its clinical effectiveness evidence, (3) its reimbursement strategy, and (4) its scope of use to HCPs. Furthermore, this study emphasises the importance of a thorough early-CEA for clinicians and policy makers.

Chapter 4: This fourth chapter uses the output from the short-term model (chapter #3) as a starting point to analyse the lifetime cost-effectiveness of *Straticyte*^{TM} among oral cancer patients from the public payer perspective. This analysis identifies the possible downstream effect on the healthcare system by conducting early-CEA using the methods identified in chapter 2. This kind of analysis helps alert decision makers of ongoing innovations, it provides preliminary clinical and economic evidence as a consequence of their adoption. This chapter in this thesis also demonstrates the importance of public funding strategy for a technology used in dental care.

Chapter 5: This last chapter provides a summary of the main findings presented in this thesis and discusses major contributions and the key limitations of this thesis, as well as directions for some future research.

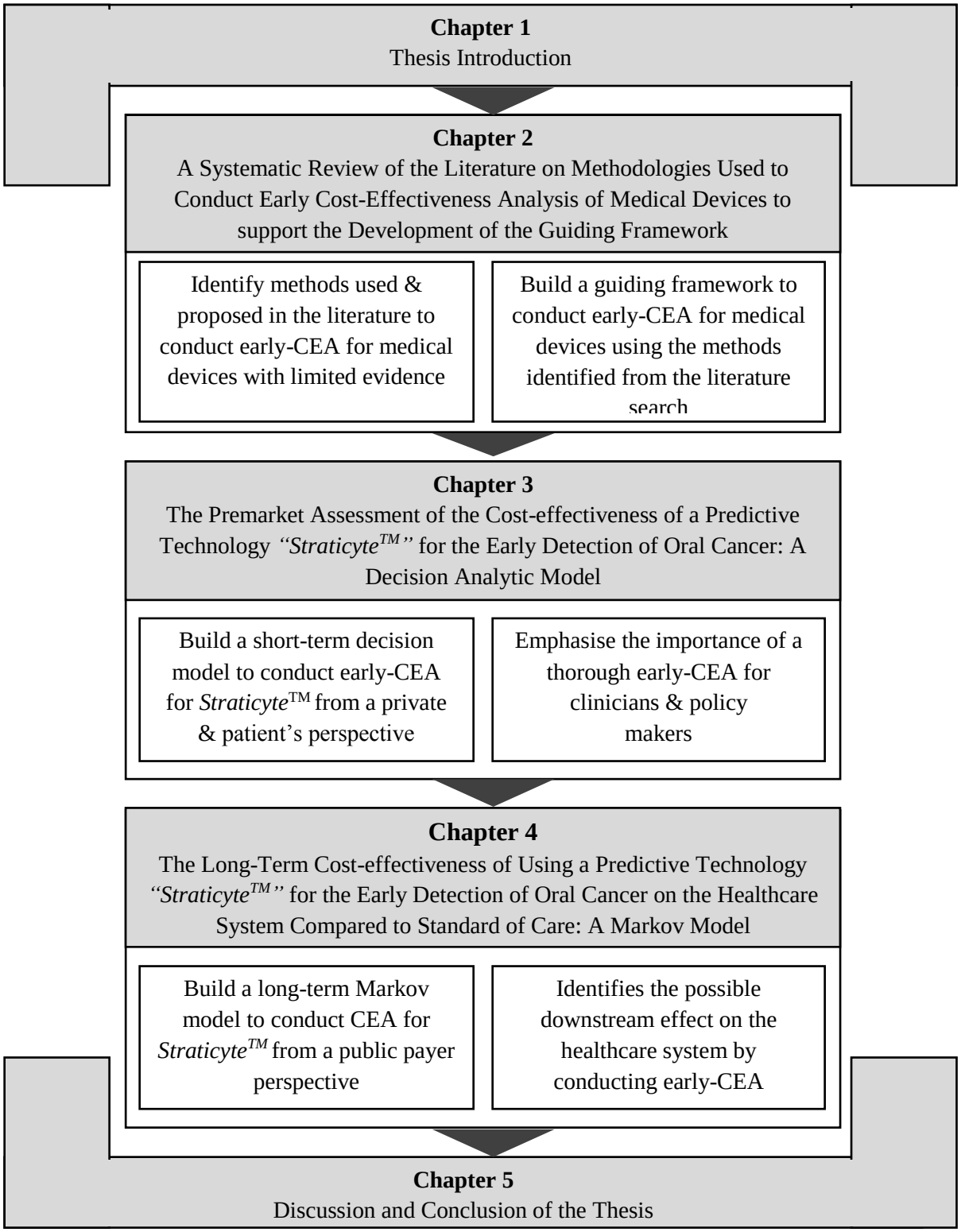

Figure 1: The Overall Structure of the Thesis.

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CHAPTER 2 -

A Systematic Review of the Literature on Methodologies Used to Conduct Early Cost-Effectiveness Analysis of Medical Devices to Support the Development of the Guiding Framework*

SHORT TITLE

Guiding framework for conducting early-CEA

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ABSTRACT

Objectives: Early cost-effectiveness analysis (CEA) is becoming an attractive approach to inform manufacturers whether to continue investing resources into developing the device and to improve a products portfolio for reimbursement stage. This review identifies and critically apprises methods for early-CEAs and proposes a conceptual guiding framework to conduct robust early-CEA for medical devices with limited evidence.

Methods: A systematic review of medical databases was conducted and two reviewers screened studies independently and in duplicate. Studies on medical devices and early-CEAs were included and grouped into 3-main categories: conceptual, application and both (i.e. conceptual and application). Furthermore, conceptual guiding framework with three key general stages was developed based on the identified methods.

Results: Of the 1,513 identified citations, 26 studies were included, of which 4 were conceptual studies, 12 application and 10 studies were both. Thirteen methods form the included 26 studies were identified and grouped based on their purpose in conducting early-CEAs. 3/13 of methods were categorized under scope and conceptual economic model, 7/13 methods dealt with the inventory of available evidence and additional data collection, and 5/13 was for early cost-effectiveness data analysis. Furthermore, using all these methods, a guiding framework of how to conduct an early-CEA for medical devices was created.

Conclusion: Increased interest in early-CEA for medical devices holds promise for key stakeholders, including manufacturers, payers, and healthcare providers. Our proposed comprehensive framework for conducting early-CEA for medical devices with limited evidence classifies and harmonizes the available methods, to support the utilization of early-CEA for key

stakeholders in medical device development and implementation. Given that medical devices have limited evidence throughout their lifecycle, this framework could potentially be used at any stage. Further application of this framework for early as well as other stages of a medical device's lifecycle is needed to validate its usefulness.

INTRODUCTION

New health technologies might add value to health systems, resulting in improved patient outcomes, convenience, and sustainability of care (1). Health technology assessment (HTA) methods have become a standard part of the decision-making processes for healthcare services (1). HTA supports decisions related to new heath technologies by taking into consideration its clinical, economic, ethical, and organizational impact on patients and society as a whole (2). Given the proviso of a limited budget and increasing innovations in health technology, greater emphasis has been put on economic evaluations (EEs) (i.e. cost-effectiveness analysis [CEA]) of new technologies when informing decisions related to their coverage and adoption in the healthcare system (3). Payer reimbursement results in wide access of new technologies in clinical practice, generating improved health for the public and return on investment for the manufacturer (1; 2).

There has been increasing interest in conducting EEs during earlier stages of a health technology's lifecycle (i.e. early-CEA) to inform decisions during product development, as well as identify potential barriers and facilitators for greater market access and appropriate pricing (2; 3). Methodological advances in early-CEA have been explored, with the majority of the literature in relation to pharmaceuticals with substantial commercial value (3; 4). Early-CEAs are less commonly conducted for medical devices, despite the fact that many years and resources are spent on research and development (R&D) of new medical devices that ultimately fail to gain adoption

(3; 4). There was, however, an increase in early-CEA studies evaluating medical devices since 2006, due to several reasons, including high R&D costs and shorter life spans of medical devices compared to pharmaceuticals (4). Further, there has been a global increase in government investment in regional medical technology innovation clusters (4).

One of the goals of early-CEA is to gain perspective on the potential barriers and facilitators for wider market penetration earlier in the products' life cycle (3). Early-CEAs inform decisions regarding the commercial viability of new medical devices, by helping inform the manufacturer whether to continue investing resources into developing the device, and if so, how to best spend resources in order to build a compelling application and increase the device's chances of reimbursement (3; 4). Conversely, if only late stage CEA is performed, manufacturers take a considerable risk, since substantial R&D investments were already made, and a potential negative reimbursement decision can have detrimental consequences (3-5).

One of the reasons that there are fewer early-CEAs for medical devices is that there is currently a lack of guidance in how to conduct them. Thus, it would be valuable to strengthen the methodological guidance around conducting early-CEA for medical devices, for both manufacturers and healthcare funders, to encourage their use and improve their quality. Cooperation between device developers, innovation clusters, and HTA research and policy groups, clinicians and patients, and continuous use and improvement of CEA methodologies, is key to developing successful medical technologies (4).

We conducted a comprehensive systematic literature review to summarize and contextualize all of the available methods for conducting early-CEAs for medical devices. The primary objective was

to identify and appraise available methods used during different stages of early-CEA. The secondary objective was to build a conceptual guiding framework on early-CEA methodology, based on both theoretical and applied methods identified in the literature. While this guiding framework is for early (premarket) CEA, given that medical devices have limited evidence at all stages of their life cycle due to their regulatory requirements, this framework may be used at other stages. The aim of our review is to provide guidance to create robust early economic models, in order to provide useful insights into the potential value of medical devices, and to help meet the requirements of late stage economic models.

METHODS

Searching for Relevant Studies

A comprehensive systematic literature search was developed by an information specialist (K.C.) and the primary reviewer (S.K.). The bibliographic databases, MEDLINE (1946-) and EMBASE (1974-) using the OVID interface, PubMed and, the Cochrane Library were searched up to September 1, 2017. Terminology was used to search controlled vocabularies (MeSH and EMTREE) and keywords on the concept of "Technology Assessment, Biomedical", "health technology", "medical technology", "early HTA", "limited evidence", "Model Economic", "Economic Evaluation", "cost-effectiveness", "assessment" (Supplementary Material 2. I). The search was limited to English, and to studies published after 1996. This date was used because studies on methods used to inform decisions in early stage economic modeling were first published (4). Grey literature was identified through searching the websites of health technology assessment and related agencies. The Google search engine was also used for additional web-based materials and information. The search term "early CEA", "early HTA", "limited evidence" and "medical

devices" were used. All searches were supplemented by reviewing the bibliographies of key papers and all search results were imported into EndNote x7 (6), for duplicate removal and reference management.

Selection Criteria for all Studies

The identified articles were screened for inclusion based on the pre-defined selection criteria (Supplementary Material 2. II). The titles and abstracts were screened independently and in duplicate (S.K and B.T.). The same reviewers screened full texts of potentially relevant articles independently and in duplicate. If consensus could not be reached, disagreements were resolved by a third author (D.O.).

Categorization of the papers

The included articles were grouped into three categories. Articles that aimed at building a framework for early-CEAs or proposed methods to conduct early-CEAs were categorized as "Conceptual" records. Articles that were case studies of early-CEAs or illustrations of theory using examples were categorized as "Application" records. Lastly, articles that both introduced a potential method and applied it to a case study were categorized as both "Conceptual" and "Application" records.

Data Extraction

A standardized data abstraction form was used by reviewers (S.K. and B.T.) to extract data from the relevant records. Reviewers abstracted descriptive information including authors' names, year of publication and study objectives. For articles categorized as conceptual records, we abstracted

the proposed assessment method, perspective that the method aims to inform, as well as the stage of product's life cycle where the method was used, if available.

For articles categorized as application records, we abstracted the perspective of the analysis, methods used to narrow the scope, type of economic model used, reports of scenario analyses and sensitivity analyses, as well as the sources of model inputs and potential methods used to collect additional inputs when there is limited or no evidence. Where applicable, in both types of records, the strengths, limitations, and rationales for using the proposed or applied methods were also abstracted.

Data Analysis and Synthesis

The abstracted data was analyzed and synthesized in a narrative summary to:

1) Identify and report the frequency of the methods proposed and applied in early-CEAs;
2) Identify the purpose of the methods proposed and/ or used to conduct early-CEA for medical devices when there is limited or no evidence;
3) Evaluate the extent to which methods can easily and effectively be used to conduct early-CEA given the context as well as the author-reported strengths, limitations, and rationales where applicable;
4) Report if the authors propose any framework in early-CEA for medical devices.

Development of the Conceptual Guiding Framework

A conceptual guiding framework was developed based on the proposed and applied methods identified in this comprehensive systematic review. First, the methods synthesized and evaluated in this paper were grouped into three key general stages of conducting early-CEA with limited evidence:

1) The scope and the conceptual economic model;
2) Inventory of the available evidence and additional data collection;
3) Early cost-effectiveness data analysis.

Second, a detailed stepwise guide was developed using the methods from the aforementioned three key general stages to help conduct early-CEAs with limited evidence for medical devices. This guiding framework organized the methods into four steps based on key tasks and information required to populate the early economic model to run the early-CEA and inform early-stage decision-making.

RESULTS

Searching for relevant studies

A total of 1,513 unique studies were identified. Of these, 141 full-text articles were reviewed and 26 studies were deemed eligible for inclusion. Of the 115 studies that were excluded, 74 were not early-CEA for medical devices, 11 were abstracts with no published manuscripts, 24 studies were not evaluating medical devices and 6 were not primary research. Study flow and reasons for exclusions are outlined in the PRISMA flowchart (Figure 1).

Study Characteristics

Characteristics of the included studies are summarized in Table 1. All studies were conducted in Europe and there were four conceptual records (4/26, 15%), twelve application records (12/26, 46%) and ten studies categorized as both "conceptual" and "application" (10/26, 39%).

The target audience was explicitly mentioned in 3/26 (12%) of included studies. For the remaining studies, it was deduced that the target audience was the manufacturer and this was based on the objectives reported by study authors. The 12 application studies reported on the potential cost-

effectiveness of medical devices of interest to manufacturers. In all of the application studies, the analyses were used to demonstrate whether the device would be cost-effective based on current available data, and whether potential future investments to gather additional clinical and economic evidence in order to support the reimbursement strategy are worthwhile. Specifically, such additional evidence contributes to creating more robust economic outputs helping support its adoption in the healthcare system. The early-CEA can also act as a method for knowledge translation and inform key stakeholders, including industry and policy makers, about potential cost-effective medical devices in the pipeline.

In addition to potential methods utilized in early-CEAs, 4/26 (15%) of the included studies, noted the need to develop a framework for early assessment of medical devices with limited evidence. Three out of 26 studies presented frameworks in early HTA that support the decision-making process in medical device development through analytical decision support techniques.

Methods in use to Conduct Early-CEA for Medical Devices

The quantitative and qualitative methods used in the included studies are presented in Table 2. Based on the steps of conducting classic EEs, these methods have been grouped into the following key stages of conducting early-CEA: (1) The scope and the conceptual economic model; (2) inventory of the available evidence and additional data collection required; and (3) early cost-effectiveness data analysis.

Thirteen unique methods were identified from the total 26 studies included in this review. These methods were grouped based on their purpose of use in conducting early-CEAs. 3/13 (23%) of the methods were categorized as scope and conceptual economic model, 7/13 (39%) of the methods dealt with the inventory of available evidence and additional data collection, and 5/13 (8%) in

stage 3, early cost-effectiveness data analysis. The methods and goals across studies were diverse, and this shows that more dimensions than costs and clinical effects are relevant in early-CEAs. Table 2, also shows the frequency of the methods used in the literature.

Stage #1- The Scope and the Conceptual Economic Model

Sequential methods such as narrowing the scope of the analysis, scenario drafting, as well as conceptualizing the health economic model were commonly proposed (21/26; 81% of the included studies) and utilized in the included studies at this stage of the evaluation.

The first step was to consider where in the healthcare system the new medical device fits, e.g. how it would be used by HCPs or patients. To explore this, one needs to determine the potential **a**pplication of the medical device, the target **p**opulation, relevant **c**omparator(s), appropriate **o**utcomes and the **i**ntervention/device under investigation. This is referred to as the APCOI approach (11; 15; 21; 30). This is simply the re-arrangement of the "PICO" method used for designing clinical research. The APCOI approach defines the problem by identifying the anticipated application of the test in the healthcare system, which in turn narrows the scope of the analysis.

Next, drafting scenarios involving the use of medical devices were a common practice in the included studies (12; 15-19; 21; 26; 30). Discussions with different stakeholders are a necessity in this step. Identifying qualitative scenario alternatives helps determine where in the healthcare system the health technology might be used. Quantifying alternative scenarios in the later stages (i.e. stage #3) can help anticipate the impact it will have on the healthcare system as well as help with the positioning of the medical device in the market. The drafted scenarios among the included studies mostly represented the likely patterns of the devices' diffusion across the health care

system, focusing on features that are still likely to change during its development such as clinical, economic, patient-reported and organizational parameters (26). This plays an important role since it helps build the model that allows the incorporation of prior-defined scenarios into the analysis for exploratory purposes.

After narrowing the scope and defining potential scenarios for the device of interest, the authors of the included studies generally conceptualized a simple economic model that was adaptable to the inevitable changes in the later stages of the product's life cycle. Simple decision trees and Markov models were proposed, and used in the included studies (7-9; 11-22; 23; 25-26; 29-31). These models are advised to reflect disease pathways and be flexible given the uncertainty of how the new device will fit in the healthcare system. Additionally, it is advised that the model is user-friendly in order to incorporate new insights and evidence as they become available at later stages of device's lifecycle.

Stage #2- Inventory of the Available Evidence and Additional Data Collection

After identifying the device's potential place in health care delivery, developing a clear decision problem, drafting several scenarios and conceptualizing the economic model, the next key stage is to populate the model with the available evidence. This has always been challenging, and given the fact that this is done at the product's early stages, there is another level of uncertainty – evidence, of any quality, is not always available for medical devices to populate the model.

Different data-gathering methods have been proposed and utilized in the included studies. Methods were driven by the therapeutic area and potential indication of the medical device of interest. The ways in which data were collected varied depending on the type of data required to populate the model, as well as the extent of missing data.

The belief elicitation method was reported in 11 (42%) of the included studies (8; 10; 11; 15-17; 21-23; 28; 30). This method gathers experts' responses via standardized interviews and questionnaires. The purpose of questions and how to address uncertainty are outlined for HCPs before eliciting their responses. Questions are carefully formulated with the help of a clinical collaborator. If necessary, given the therapeutic area and the medical device, calibration methods may also be used to explain potential heterogeneity among HCPs, such as years of experience (28). Given the scarcity of the evidence, this method can help determine uncertain priors (i.e. one's beliefs about an uncertain quantity before some evidence is taken into account) for the model. Therefore, its use is often suggested in constructing Bayesian priors regarding the expected efficacy of the medical device of interest (28). Additionally, the outcome of the belief elicitation method can also be used qualitatively depending on the type of data required to populate the model. Such as helping understand the device's application, and potential impact in clinical practice by users.

The headroom method was another method that was used in seven (27%) studies (7; 8; 10; 14; 22; 23; 27). This method is used to identify the potential areas of improvement that the new device will have over the current technology (e.g. cost-savings and increased clinical effectiveness) in order to estimate its monetary value. The type of analysis used in this method depends on the available evidence of the current technology, which the new device aims to substitute or compete with. It also depends on factors that experts believe would impact the cost and the effectiveness of the new device. These methods provide a bound on the maximum reimbursable price that will then be compared with the expected cost of the device at the early stage.

Finally, the analytic hierarchy process (AHP) was another method proposed and used in three (12%) studies (9; 24; 25). This method was used to evaluate the possible success of a medical device in clinical practice. It allows for comparing the expected performance of a medical device based on preliminary data, with the established performance of the standard of care (SOC) given its application in the disease pathway or clinical practice (9; 24; 25). The outcome of this analysis allows us to determine the most promising area of application of the medical device in the health-care system.

Stage #3- Early Cost-Effectiveness Data Analysis

Compared to analyses conducted in classic CEA, the included studies suggested a few other considerations and additional potential analyses, such as exploratory analysis and value of information (VOI) analysis. It was suggested that these be conducted in an iterative manner and adjusted or updated as more evidence becomes available.

Base case, one-way sensitivity analyses (OWSA) and probabilistic sensitivity analyses (PSA) were suggested to be conducted and reported in a similar manner to classic CEAs. One modification that has been proposed by Vallejo-Torres et. al, 2011 (23) was conducting 5,000 instead of 1,000 Monte Carlo (MC) simulations in order to address the additional level of uncertainty that is inherent to early-CEA.

Exploratory analysis, also referred to as scenario analysis, was often conducted in early-CEA, which is not very common for classic CEAs. Twelve (46%) studies reported using this type of analysis. It is more common to conduct exploratory analysis for early-CEA, since the indication

of the medical device under investigation is not yet confirmed, hence requires testing of different clinical pathways.

Finally, emphasis has been put on VOI analysis among six (23%) included studies. Given that the device is being evaluated at earlier stages, additional studies may be conducted to strengthen the evidence and decrease uncertainty in the future economic model.

The Conceptual Guiding Framework

The methods identified, evaluated, and grouped into three key general stages of conducting early-CEA were used to develop a conceptual guide to help conduct robust early-CEA for medical devices and help inform key stakeholders about potential cost-effective medical devices in the pipeline. Considering all of the proposed methods in the included studies, a flowchart, or guiding framework, of how to conduct an early-CEA for medical devices was created (Figure 2). The method introduced at each step was based on the aim of that specific step for conducting early-CEA.

Steps under stage 1 were organized in a consecutive manner. For example, the problem needs to be defined by narrowing the scope first, followed by identifying and defining additional potential scenarios where the medical device can be utilized and once these are clearly identified and defined, the early-stage economic model is to be developed. However, the steps within stage 2 and stage 3 can be conducted at any order but you must complete stage 2 before proceeding to stage 3. Steps under stage 2 will allow you to gather model inputs as necessary which feeds into stage 3 where you run the model and conduct different types of analyses after populating it with the model inputs identified from the steps in stage 2. Once the appropriate analyses are conducted and an

early-CEA report is created, based on the output, the manufacturer decides to proceed to payers if the outcome is robust and acceptable and if not, they can go back to stage 2 where they try to gather more evidence in order to produce firmer estimates of cost-effectiveness to increase the chance of its adoption in the healthcare system.

DISCUSSION

Conducting early-CEA to evaluate emerging non-drug health technologies (e.g.,. medical devices) has become more prevalent in recent years, due to increasing pressure on the healthcare system, consumer demand, the complexity of biomedical R&D, the high costs of product development and the lack of patent protection for market exclusivity. Early-CEA has been of particular interest among key stakeholders, including manufacturers, for assessing the cost-effectiveness of medical devices, since a barrier to adopting new devices is often due to insufficient evidence necessary to meet regulatory requirements for market entry. Early-CEA has been shown to help this by identifying crucial data gaps prior to the market launch of the medical device, and using an iterative process will provide progressively firmer estimates of cost-effectiveness by incorporating newer data as it becomes available. The potential for early-CEA to make medical device innovation a more efficient process has spurred research interest in early-CEA methodology in this area.

This study summarized all of the available published evidence on early-CEA for medical devices for proposed methods used in early-CEA. Additionally, we developed conceptual guiding framework to conduct early-CEA using the proposed methods identified from the literature. A total of 26 records were included in this review, in which 13 unique methods, with specific applications, were identified.

Study Findings in the Context of Existing Literature

We concluded that one of the most important, yet challenging, steps in conducting early CEA is trying to populate the model with limited evidence available, which was corroborated by previously published reviews (2; 4). Early CEA is typically characterized by scarcity of empirical data, thus early health economic models need to be populated with alternative sources of information. The headroom method and the belief elicitation method, were typically suggested as potential sources of information, however these approaches can be a source of additional uncertainty to the early-CEA output.

The headroom method helps determine the maximum reimbursement price that will then be compared with the expected cost of the device at the early stage. However, it is important to acknowledge that multiple other issues need to be considered when gathering missing information during the early stages of a product's lifecycle, such as the impact it will have on product's portfolio and development uncertainty (4). On the other hand, the belief elicitation method, which was utilized 11 times in the literature, poses another challenge. Despite the fact that this method helps populate the model with specific information that is not available in the literature, certain model inputs, such as the clinical performance of technologies, is difficult to quantify. Given this method uses opinions of experts to synthesize evidence, there is a tendency to underestimate uncertainty about quantitative information and overestimate model inputs such as the probability of a technology's effectiveness (4). Other early CEA methods such as, scenario drafting, analytic hierarchy process, Bayesian evidence synthesis and VOI analysis identified in this review, show promise as being easier to use and more informative.

Based on a review of the literature, a detailed conceptual guiding framework for conducting early-CEA of medical devices was developed. This framework includes 13 unique methods, which were organized based on their purpose. This framework aligns with the foundation of previously proposed frameworks (7; 26; 29; 30).

The proposed framework in this paper does include the general stages of conducting early-CEA that has been presented in the literature, but it also further includes specific methods used in early-CEA to help inform users of how various methods could be used during different stages of conducting early-CEA for medical devices. Once this framework gets validated over time it can potentially allow us to understand more about the actual influence of the methods used in conducting early-CEA on the decision-making process.

Implications of Early-CEA and Application of the Conceptual Guiding Framework

Early CEA for medical devices enhances the transparency about upcoming non-drug health technologies value for money, reduces the information asymmetry between drugs and devices prevalent in the market, and can also potentially help shape the reimbursement landscape of medical devices.

Using a conceptual guiding framework may have a significant impact on the reimbursement landscape by informing decision-making by both industry and government. From the industry perspective, early CEA may be used for early market assessment, managing R&D portfolios, and informing the pricing and reimbursement scenarios (3; 5). These practices may help with the value proposition of the device to potential payers, and as a result improve chances of widespread implementation in clinical practice (3; 5). From the policy perspective, decision-makers may benefit from the early exposure to the potential cost-effectiveness of the technology. This may

facilitate the decision-making process, as decision-makers could incorporate the value and economic properties of an innovation into their current decision-making, forecasting, and anticipation of future technological development.

Limitations and Strengths

This study has several limitations. First, given that the field of early CEA is still emerging, different terminologies have been used in the literature, which may have resulted in some relevant studies being missed in our search. To mitigate this, we conducted a pilot search and gathered additional keywords to further develop our search strategy. Another limitation is that there could be early CEA methods used for drugs that may potentially be applicable to medical devices, however, these were not investigated as this was beyond the scope of this review. Lastly, the framework developed in this study has not been validated, thus conclusions from this framework should be carefully considered.

This study has several strengths. First, the literature review was extensive since it looked for studies in five different databases, grey literature, searching the references of all included studies, and recommendations from experts in this field. Second, the available methods were categorized into three key stages of conducting early CEA based on their aims, for easier interpretation. Third, we developed a conceptual framework for conducting early CEA for medical devices, to help guide potential modelers and to try to standardize the methods.

Conclusion and Suggestions for Future Research

Decisions on coverage and adoption of medical devices in healthcare systems are difficult, notably because of the limited clinical evidence available relevant to current regulatory requirements for market entry. Increased interest in early CEA for medical devices holds promise for key

stakeholders, including manufacturers, payers, and healthcare providers, to make more informed decisions. In turn, this may improve the efficiency of medical device development, and improve the chance of successful and wider implementation. Given that medical devices have limited evidence throughout their lifecycle, this framework could potentially be used at any stage. Furthermore, a framework by the IDEAL Collaboration which is mainly for surgical procedures, describes the stages through which interventional therapy normally passes, the characteristics of each stage as well as it recommends a potential most appropriate study design (33). Future research to validate and further develop the framework given other frameworks in mind, both for the early and also other stages of the product's life cycle, will be essential to improve the CEA process for medical devices.

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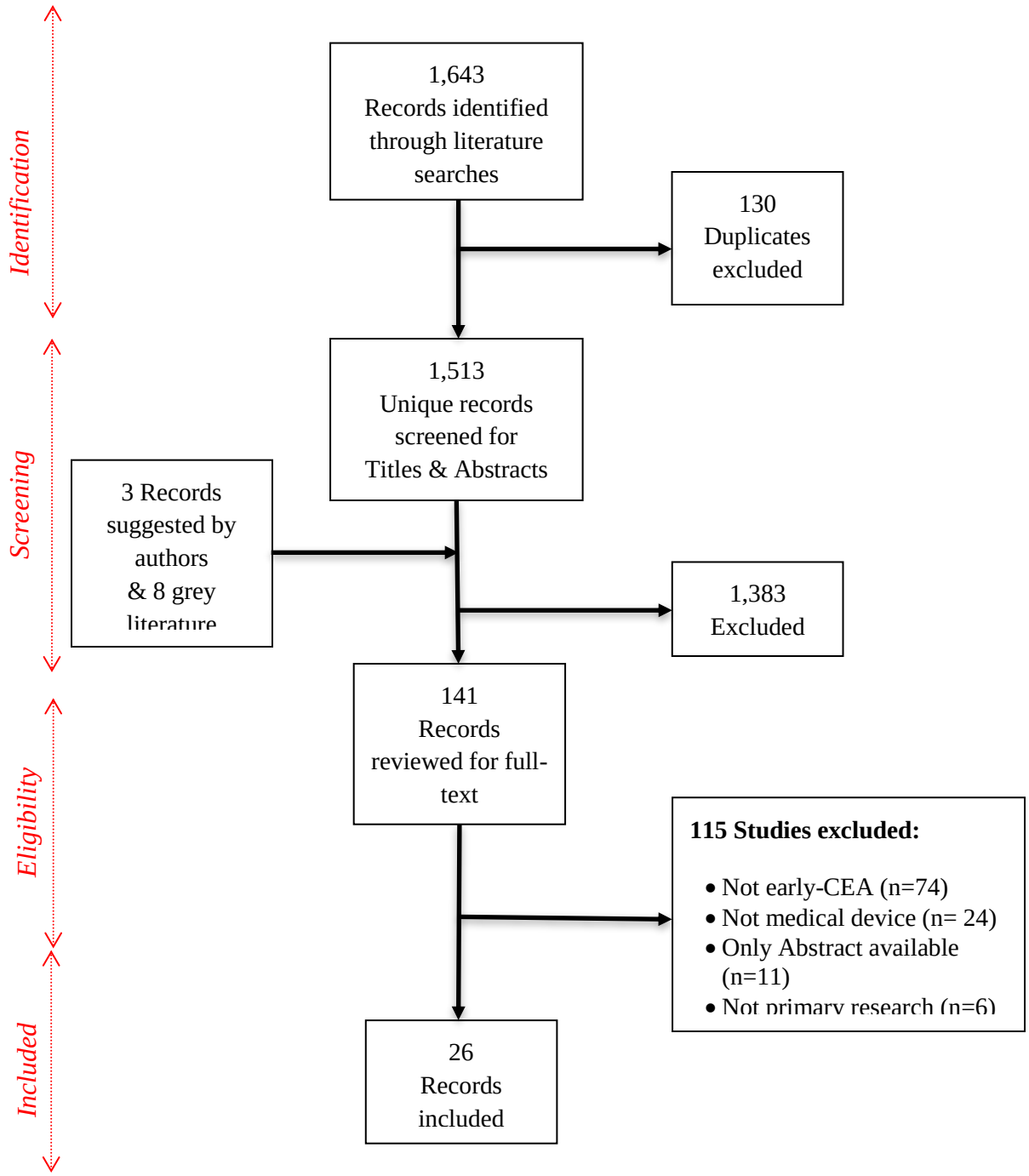

Figure 1: The PRISMA Flowchart of Reasons for Excluding Studies.

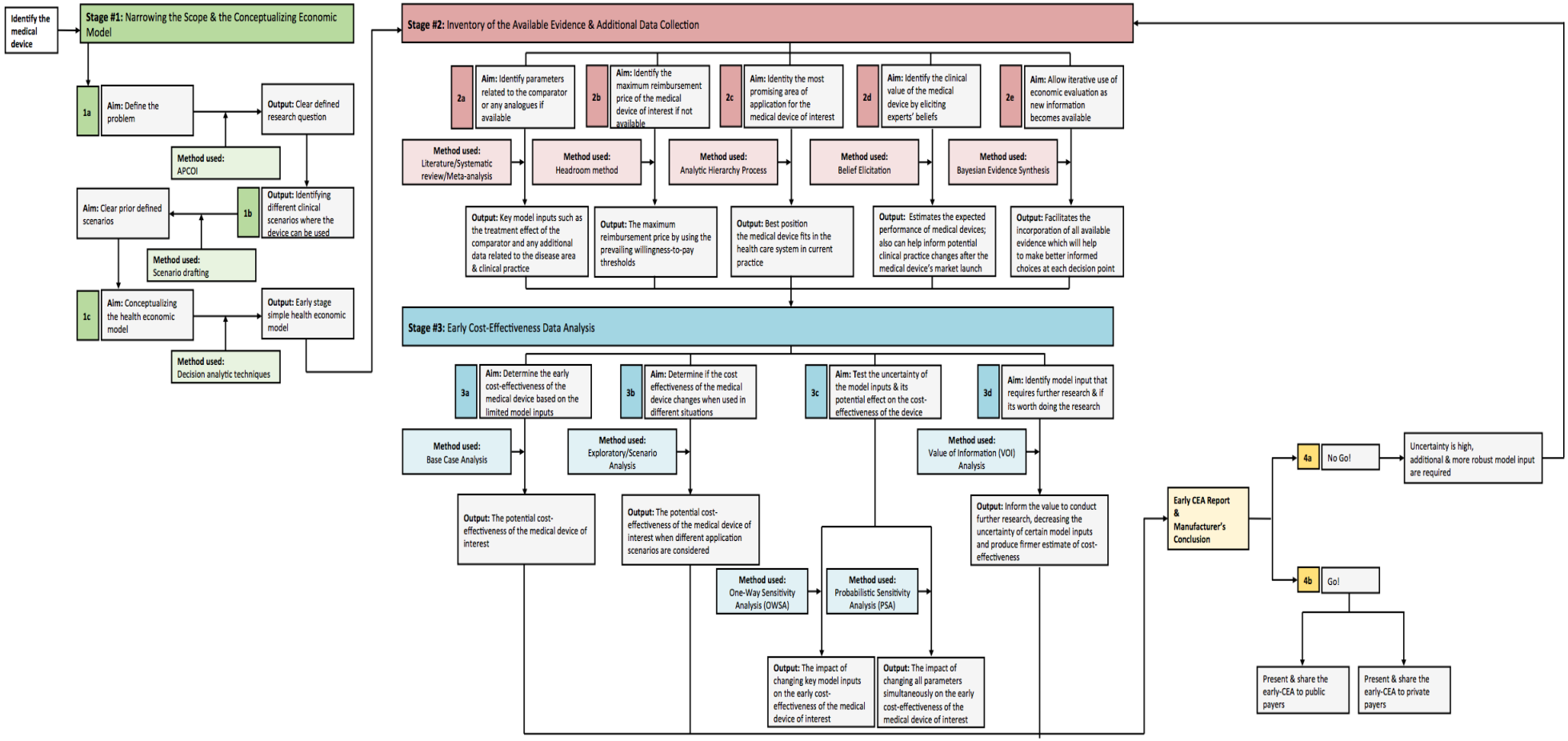

Figure 2: The Conceptual Guiding Framework for Conducting Early-CEA for Medical Devices When There is Limited Evidence.

Table 1: Study Characteristics of the Included Studies.

Author, Year	Country	Aim of the Study
(A) Conceptual Records		
Sculpher, 1997	UK	• Present an iterative economic evaluation framework
Vallejo-Torres, 2008	UK & Netherlands	• Present the use of an iterative Bayesian approach to inform early decisions regarding medical devices
Pecchia, 2012	UK	• Present AHP and early stage economic evaluation to conduct early stage evaluation of biomedical devices
Markiewicz, 2017	Netherlands	• Analyze how manufacturers perform early assessment of medical devices to allow them to meet the requirements of potential stakeholders
(B) Application Records		
Cao, 2013	Netherlands	• Conduct early cost-effectiveness analysis for a novel point-of-care testing device in health failure disease management by combining probability elicitation with early health economic modeling
Koeber, 2013	Germany	• Demonstrate a practice-oriented approach, four steps of simple early stage modeling
Brandes, 2015	Germany	• Generate an early estimate of value to identify attractive target patient groups, inform tentative value-based prices for different assumptions of effectiveness and also derive implications for including such value considerations into product design
De Windt, 2016	Netherlands	• Conducted an early health economic model and analysis to identify key parameters that drive cost-effectiveness, define targets for both product costs and utilities and support further health economic developments
Buisman, 2016	Netherlands	• Early CEA to evaluate the cost and health effects of new and current diagnostic test strategies from a societal perspective in patients with IA who are suspected of having RA
Luime, 2016	Netherlands	• Assess the short term early cost-effectiveness of four add-on diagnostic tests in early inflammatory arthritis patients at risk of RA
Kip, 2016	Netherlands	• Build an early economic model using expert's judgment about improved test performance as model inputs to estimate the early cost-effectiveness of adding a copeptin and H-FABP test to conventional serial HsTn measurement, to allow rapid exclusion of acute myocardial infarction (specifically NSTEMI) in the coronary pain unit
Van Til, 2006	Netherland	• Conduct an early CEA of interventions for chronic hemiplegic shoulder pain
Schwander, 2014	Germany	• Determine the cost at which the next generation AVDs are to be regarded as cost-effective
Dong, 2006	UK	• Conduct an early CEA of TKR using computer-assisted surgery
Huygens, 2016	Netherlands	• Develop a decision analytic model for early HTA of tissue engineered heart valves
Wetering, 2012	Netherlands	• Conduct an early assessment of a point-of-care chip for the detection of a pathological deviation of the potassium levels in patients at increased risk
(C) Both (Conceptual & Application) Records		

Vallejo-Torres, 2011	UK & Netherlands	• Apply the Bayesian Economic Evaluation method in the development process of new medical devices
Hilgerink, 2011	Netherlands	• Quantify the potential clinical value of different scenarios incorporating PA imaging by means of Analytic Hierarchy Process (AHP)
Hummel, 2012	Netherlands	• Predict the health economic performance of a new NFS treatment, where AHP was used to support the missing NFS performance data
Retel, 2012	Netherland	• Explore the value of developing a multi-parameter framework to assess dynamic aspects of a technology still in development by means of scenario drafting and determine the effects and cost-effectiveness of possible future diffusion patterns on the case of the clinical implementation of 70-gene signature of breast cancer
Chapman, 2013	UK	• Present the headroom method by applying it to a diverse set of case studies
Haakma, 2014	Denmark	• Investigate a belief elicitation method for estimating diagnosis performance in the early stages of development of PAM imaging versus MRI for detecting breast cancer
Retel, 2013	Netherlands	• Present a framework to simultaneously support decisions concerning adoption, further development, and research from a societal perspective
Buisman, 2016	Netherlands	• Develop a framework with general steps of early-CEAs of new medical tests and apply it to two cases
Craven, 2009	UK	• Develop a cost-effectiveness tool in Microsoft® Excel software and applied it to a case study to conduct early CEA
Tarricone, 2011	UK	• Use an early CEA for TAVI to explore the implications of assessing medical devices

AHP: Analytic Hierarchy Process; AVDs: Artificial vision devices; CEA: Cost-effectiveness Analysis; H-FABP: heart-type fatty acid binding protein; HsTn: high-sensitivity troponin; IA: Inflammatory arthritis; MRI: Magnetic resonance imaging; NFS: Non-fusion surgical treatment; NSTEMI: non– ST elevation myocardial infarction; PA: Photoacoustic; PAM: photo acoustic mammography; RA: Rheumatoid arthritis; TAVI: Transcatheter aortic valve implementation; TKR: Total knee replacement; UK: United Kingdom

Table 2: Frequency of the Methods Described and Utilized in the Literature when Investigating Early-CEA of Medical Devices.

	Three Key Stages of Conducting Early Economic Evaluations												
	Narrowing the Scope & the Conceptualizing Economic Model			**Inventory of the Available Evidence & Additional Data Collection**					**Early Cost-Effectiveness Data Analysis**				
	APCOI	Scenario Drafting	Simple economic model	Literature/Systematic review/Meta-analysis	Headroom method	Analytic Hierarchy Process	Belief Elicitation	Bayesian Evidence Synthesis	Base Case Analysis	One-Way Sensitivity Analysis	Probabilistic Sensitivity Analysis	Exploratory/ Scenario Analysis	Value of Information Analysis
(A) CONCEPTUAL													
Sculpher, 1997			✓	✓	✓								
Vallejo-Torres, 2008			✓	✓	✓		✓	✓		✓			✓
Pecchia, 2012			✓			✓							
Markiewicz, 2017				✓	✓		✓						
(B) APPLICATION													
Cao, 2013	✓		✓	✓			✓		✓		✓		
Koeber, 2013		✓	✓	✓					✓	✓		✓	
Brandes, 2015			✓	✓					✓	✓		✓	
De Windt, 2016			✓	✓	✓				✓	✓		✓	
Buisman, 2016	✓	✓	✓	✓			✓		✓	✓	✓	✓	
Luime, 2016		✓	✓	✓			✓		✓	✓	✓	✓	
Kip, 2017		✓	✓	✓			✓		✓	✓	✓	✓	
Van Til, 2006		✓	✓	✓					✓		✓	✓	
Schwander, 2014		✓	✓	✓					✓	✓	✓	✓	
Dong, 2006			✓	✓					✓	✓	✓		
Huygens, 2016	✓	✓	✓	✓			✓		✓	✓		✓	
Wetering, 2012			✓	✓	✓		✓		✓	✓	✓		✓
(C) BOTH (CONCEPTUAL & APPLICATION)													
Vallejo-Torres, 2011			✓	✓	✓		✓	✓	✓	✓	✓		✓
Hilgerink, 2011						✓							
Hummel, 2012			✓	✓		✓			✓	✓		✓	
Retel, 2012		✓	✓	✓					✓	✓	✓	✓	
Chapman, 2013					✓								
Haakma, 2014							✓						
Retel, 2013			✓							✓	✓		✓
Buisman, 2016	✓	✓	✓	✓			✓		✓	✓	✓	✓	✓
Craven, 2009			✓							✓			
Tarricone, 2011								✓					✓
Frequency of the Methods	**4**	**9**	**21**	**19**	**7**	**3**	**11**	**3**	**16**	**17**	**12**	**12**	**6**

**APCOI: Application, population, comparator, outcome and intervention*

Supplementary Material 2. I – The Literature Search Strategies

OVERVIEW	
Interface:	OVID
Databases:	MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)*1946 to Present*
Date of Search:	September 1st,2017

DATABASE STRATEGY		
#	**Searches**	**Results**
1	*Technology Assessment, Biomedical/	8594
2	*Biomedical Technology Assessment/ use oemezd	3792
3	((health technology or health technologies or medical technology or medical technologies) adj2 assessment*).ti,ab.	5587
4	(technolog* or equipment* or device?).ti,ab.	1094724
5	exp *medical/ or health*.ti,ab.	3957317
6	4 and 5	162922
7	1 or 2 or 3 or 6	168737
8	(early* or earlie*).ti,ab.	2901306
9	"early HTA".ti,ab.	7
10	“limited evidence”.ti,ab.	10717
11	8 or 9 or 10	2901306
12	exp *Models, Economic/	19115
13	*Models, Statistical/	39203
14	*Statistical Model/ use oemezd	15438
15	model*.ti,ab.	4035474
16	Cost-Benefit Analysis/	129449
17	"Cost Effectiveness analysis"/ use oemezd	102460
18	(cost-effectivene* or economic evaluation*).ti,ab.	97144
19	(approval or assessment or value* or cost*).ti,ab.	4999357
20	19 and 5	866337
21	12 or 13 or 14 or 15 or 16 or 17 or 18 or 20	4944576
22	7 and 11 and 21	6673
23	limit 22 to yr="1996 -Current"	4852
24	limit 23 to english language	3352
25	Remove duplicates from 24	1520

OVERVIEW	
Interface:	OVID
Databases:	EMBASE 1974 to 2014 November 06
Date of Search:	September 1st, 2017

Database Strategy		
#	**Searches**	**Results**
1	*Technology Assessment, Biomedical/ use prmz	4623
2	*Biomedical Technology Assessment/ use oemezd	3750
3	((health technology or health technologies or medical technology or medical technologies) adj2 assessment*).ti,ab.	4890
4	or/1-3	11837
5	(early* or earlie*).ti,ab.	2720369
6	exp *Models, Economic/ use prmz	3434
7	*Models, Statistical/ use prmz	21369
8	*Statistical Model/ use oemezd	14589
9	model*.ti,ab.	3708210
10	Cost-Benefit Analysis/ use prmz	59464
11	"Cost Effectiveness Analysis"/ use oemezd	96383
12	(cost-effective* or economic evaluation*).ti,ab.	183232
13	or/6-12	3937841
14	4 and 5 and 13	308
15	limit 14 to yr="1996 -Current"	234
16	limit 15 to english language	225

OVERVIEW	
Databases:	The Cochrane Library
Date of Search:	September 1st, 2017

Database Strategy		
#	**Searches**	**Results**
1	Technology Assessment and Biomedical	575
2	(health technology or health technologies or medical technology or medical technologies) near/2 assessment*:ti,ab,kw	721
3	1 or 2	1188
4	early* or earlie*:ti,ab,kw	54474
5	Models, Economic	1900
6	Models, Statistical	1316

7	model* or cost-effective* or economic evaluation*:ti,ab,kw	63522
8	5 or 6 or 7	67934
9	3 and 4 and 9	22

OVERVIEW	
Databases:	PubMed
Date of Search:	September 1st, 2017

Database Strategy		
#	**Searches**	**Results**
1	((((early cost effectiveness analysis[Title/Abstract]) OR early health technology assessment[Title/Abstract]) OR early economic evaluation)) AND medical device[Title/Abstract]	6

Supplementary Material 2. II – The Study Selection Criteria

The following inclusion/ Exclusion criteria were used to conduct Level 1 screening (i.e. titles and abstracts review) and Level 2 screening (i.e. full text review) of potentially relevant articles from the systemic literature search results.

1. Is the study within Health care context?
   Yes (INCLUDE)
   No (EXCLUDE)
   Can't decide (INCLUDE)*

2. Does the study report on the early assessment of medical devices/ health technology (medical devices/ health technology = an instrument, apparatus, implant, in vitro reagent, but does not achieve its purpose through chemical action within or on the body)?
   Yes (INCLUDE)
   No (EXCLUDE)
   Can't decide (INCLUDE)*

3. Does the study report on practice of early economic evaluation?
   Yes (INCLUDE)
   No (EXCLUDE)
   Can't decide (INCLUDE)*

4. Does the study report on practice and or theory of methodology for early health technology assessment?
   Yes (INCLUDE)
   No (EXCLUDE)
   Can't decide (INCLUDE)*

5. Is the publication not a study (commentary, letter, conference proceedings)?
   Yes (EXCLUDE)
   No (INCLUDE)
   Can't decide (INCLUDE)*

**In level 1 screening when reviewers cannot make a decision, by default they included the study for further screening (i.e. Level 2). Additionally, when the full text of potential relevant studies are screened in Level 2 and consensus could not be reached between the two independent reviewers, their disagreements were resolved by a third reviewer.*

CHAPTER 3 -

The Premarket Assessment of the Cost-Effectiveness of a Predictive Technology *"Straticyte™"* for the Early Detection of Oral Cancer: A Decision Analytic Model *

SHORT TITLE

Early-CEA of a Predictive Technology *"StraticyteTM"*

AUTHORS

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**Khoudigian-Sinani et al. The Premarket Assessment of the Cost-Effectiveness of a Predictive Technology "Straticyte™" for the Early Detection of Oral Cancer: A Decision Analytic Model. Health Econ Rev, 2017;7(1): 35-43.*

ABSTRACT

Introduction: Approximately half of oral cancers are detected in advanced stages. The current gold standard is histopathological assessment of biopsied tissue, which is subjective and dependent on expertise. *Straticyte*^{TM}, a novel prognostic tool at the premarket stage that more accurately identifies patients at high risk for oral cancer than histopathology alone. This study conducts an early cost-effectiveness analysis (CEA) of *Straticyte*^{TM} and histopathology *versus* histopathology alone for oral cancer diagnosis in adult patients.

Methods: A decision-analytic model was constructed after narrowing the scope of *Straticyte*^{TM}, and defining application paths. Data was gathered using the belief elicitation method, and systematic review and meta-analysis. The early CEA was conducted from private-payer and patient perspectives, capturing both direct and indirect costs over a five-year time horizon. One-way and probabilistic sensitivity analyses were conducted to investigate uncertainty.

Results: Compared to histopathology alone, histopathology with *Straticyte*^{TM} was the dominant strategy, resulting in fewer cancer cases (31 versus 36 per 100 patients) and lower total costs per cancer case avoided ($3,360 versus $3,553). This remained robust when *Straticyte*^{TM} was applied to moderate and mild cases, but became slightly more expensive but still more effective than histopathology alone when *Straticyte*^{TM} was applied to only mild cases. The probabilistic and one-way sensitivity analyses demonstrated that incorporating *Straticyte*^{TM} to the current algorithm would be cost-effective over a wide range of parameters and willingness-to-pay values.

Conclusion: This study demonstrates high probability that *Straticyte*^{TM} and histopathology will be cost-effective, which encourages continued investment in the product. The analysis is informed by limited clinical data on *Straticyte*^{TM}, however as more data becomes available, more precise estimates will be generated.

INTRODUCTION

Economic evaluations (EEs) are increasingly used to inform decisions of healthcare resource allocation for interventions, including drugs and medical devices (1). EEs, primarily cost-effectiveness analyses (CEA), are done for reimbursement in the late stages (i.e. post-market) of an intervention's development. Reimbursement facilitates wide implementation in clinical practice, which improves return on investment and patients' access to care. Recently, there has been interest in conducting early (i.e. premarket) CEA, which gives companies feedback from content experts and stakeholders during their development and premarket process (2). Early CEA better prepares the company for licensing and adoption of the product, and may increase the likelihood of reimbursement by building a stronger evidence portfolio (2, 3). Late CEA is a one-time process, whereas early CEA is iterative (4). There are currently no guidelines in place on conducting early CEA, however several qualitative and quantitative approaches have been proposed (Supplementary Material 3. I).

Oral cancer encompasses cancers of the lip, oral cavity, or oropharynx, and accounts for 3% of all cancers worldwide (5, 6). Though less common in Canada, 4,100 new cases were estimated in 2013. The overall incidence in Canada is an estimated 12 cases per 100,000 people per year in men, and 5 per 100,000 in women (7, 8). Up to 50% of oral cancers are not detected until the disease is well advanced and the overall survival rate, five years after diagnosis, is about 62% (6, 8). Mortality can be reduced if treatment is initiated at an early stage, thus early diagnosis is critical.

The current gold standard for diagnosis is histopathologic assessment of a tissue biopsy, which is subjective. *Straticyte*^{TM}, a biomarker, is a novel prognostic tool for oral cancer. Based on an evaluation of 107 cases of dysplasia, with up to 10 years of follow-up, *Straticyte*^{TM} and

histopathology demonstrated improvement in both the positive predicted value (PPV) and the negative predicted (NPV) value by 10% and 27%, respectively, compared to histopathology alone, thus more accurately identifying patients at high risk (9). *Starticyte™* is first in its class, however, there is limited data regarding its effectiveness, potential use in clinical practice, and costing estimates.

Accurate predictions of true oral cancer could extend length of life, reduce morbidity with less traumatic surgeries, increase the duration of productive work lives, and save healthcare costs (35, 36). Support for its adoption rests on demonstrating value for money, as *Straticyte™* will require an investment by private sectors, since public payers do not cover it. Based on the CEA, the manufacturer, healthcare system, and individual patient will be informed whether investing in this product is worthwhile. The aim of this study is to conduct an early CEA of adding *Straticyte™* to the current standard of care for diagnosing malignant oral lesions in adults.

METHODS

The development of the economic model to determine the cost-effectiveness of *Straticyte™* is summarized in Figure 1 and described below.

Step #1: Scope, Conceptual Economic Model and Scenario Drafting

Scope: The potential application of *Starticyte™* in the healthcare system has been assessed through a comprehensive literature search and discussions with test developers, clinicians, and experts in the field of oral cancer. Using this information and the limited available evidence on *Straticyte™*, we narrowed the scope of this CEA by defining the Application, Population, Comparator, Outcome, and Intervention (APCOI) (Supplementary Material 3. II) (4). This CEA was conducted

over a time horizon of five-years and from private payer's and patient's perspectives, to capture all relevant differences in future direct and indirect costs and outcomes associated with oral pre-cancer.

Conceptual economic model: A five-year CEA was conducted using a decision analytic tree to determine whether a prognostic algorithm for oral cancer that includes *Stratictye™* compared to Histopathology alone in Canada is cost-effective. The model was build using Microsoft Excel ® based on four key assumptions (Supplementary Material 3. III) and consists of two arms (Supplementary Material 3. IV). The future costs and outcomes that occur beyond one year associated with both arms were discounted at an annual rate of 5% (10).

Scenario drafting: *Straticyte™* indication is not yet finalized, different application paths for *Straticyte™* are possible, hence scenario drafting (11) was used to assess the dynamic aspects of this health technology. In addition to the base case analysis, the effect, cost and cost-effectiveness of two additional possible scenarios where *"Straticyte™"* can successfully be applied were also explored.

Step #2: Inventory of Available Evidence and Additional Data Collection on Histopathology and *Straticyte™*

The model parameters in Table 1 were gathered from published clinical and economic literature, grey literature, and expert opinion.

Probabilities: The data used in this model was derived from a retrospective study of 107 cases of dysplasia in Canada (12). Oral dysplasia biopsy samples were assembled from archives of an oral pathology laboratory (12). All subjects with histopathological evidence of dysplasia and follow-up information for at least five-years were included. The two primary clinical outcomes were

dysplasia progression to cancer, and time in months of dysplasia progression to cancer. These cancer cases were outcomes from patients who have not undergone excision (i.e. surgery) (12). The uncertainty in probabilities of going from one state to another was modeled using both Dirichlet and Beta distribution for the purpose of probabilistic sensitivity analysis (PSA) (13). Where there was a count of zero cancer cases we did not sample from the Dirichlet distribution, instead we assumed constant zero. This was done since there was no information (i.e. observation) on the probability of developing oral cancer in the retrospective study (12).

Relative risk (RR) of malignant transformation: To inform the parameter of RR of developing cancer given treatment modality (i.e. relative risk of developing cancer given patients have undergone excision vs. no excision), we conducted a comprehensive systematic literature search to identify clinical studies that investigated the malignant transformation rate (MTR) given treatment modality (Supplementary Material 3. VI). The MTRs from the included studies were pooled and the RR of malignant transformation over 5 years was determined using the Cochrane Collaboration Review Manager Analysis version 5.2 Statistical Software (RevMan 5.2). The methodology and detailed results of this review can be found in Supplementary Materials 3.VII and 3. VIII.

Clinical practice by oral and maxillofacial (O&M) surgeons: The belief elicitation method was used to determine the potential impact of *Straticyte*^{TM} on clinical practice (14). Our objective was to determine how O&M surgeons would treat patients with oral dysplasia given the results from *Straticyte*^{TM} *and* histopathology versus histopathology alone. Questionnaires were administered face-to-face, requiring 15-30 minutes to complete, to four O&M surgeons with a minimum of five years of experience in treating patients with oral pre-cancerous lesions (Supplementary Material-3. IX). A standardized script was used, explaining the process and the purpose. Questions were

prepared with the help of a clinician, and clarified with participants. The outcomes of the elicitation (Supplementary Material 3. X) dictated where in the decision tree (i.e. which branch) the RR of developing oral cancer given excision and the associated costs and resources are applied.

Costs and resources: The costs and resource utilizations were gathered from several sources (Table 1). All costs are reported in 2014 CAD, and, if necessary, were corrected by the Canadian consumer price inflation index using the Bank of Canada online inflation calculator (15). The direct costs associated with the intervention and illness included in this CEA was as follows: oral biopsy (excision, following-up patients), pathology (technician, preparation of report), *Straticyte*^{TM} (running the test, technician, reporting the outcome, administrative cost of O&M surgeon and pathologist), pain medication, and gingivitis treatment (Supplementary Material 3. XI). The main indirect costs that were included in this CEA were the costs associated with absenteeism from work and transportation costs, included the cost of travel and parking (16, 17).

Step #3: Early Cost-Effectiveness Data Analysis

Base case and exploratory scenario analyses: CEAs were conducted in both base-case and scenario cases. This CEA investigated the costs associated with cancer cases avoided. The incremental cost is compared to the incremental health effects (18). In the base case scenario, this was the number of cancer cases avoided given the application of *Straticyte*^{TM} to all three categories (i.e. Severe, Moderate, Mild) classified by histopathology. In addition, we explored the effect, cost, and cost-effectiveness of two alternative scenarios where *"Straticyte*^{TM}*"* can be applied. For exploratory scenario #1, we examined the number of cancer cases avoided when *Straticyte*^{TM} was applied to two categories, moderate and mild cases, and for exploratory scenario #2, we examined cases avoided when *Straticyte*^{TM} was applied to only mild cases.

Sensitivity analyses: To explore the uncertainty around parameters in the model to find the inputs with the largest impact on the model outcome, one-way sensitivity analyses (OWSA) and probabilistic sensitivity analyses (PSA) were conducted (13). OWSA provides insight into alternative values for specific parameters that could make a meaningful impact on the model outcome and on the potential decision based upon it. Given this, OWSA was conducted for some of the fixed parameters such as the discount rate, number of follow-ups in a year. The upper and lower values for all included parameters were obtained from published literature. If not available, the mean ±20% was considered a reasonable range to evaluate a model parameter in the deterministic model. Furthermore, PSA was conducted to take account the overall uncertainty from the combined variability of several factors. A Monte Carlo (MC) simulation method was used to compute the results (13). A total of 5000 simulations were completed given the fact that early CEAs have an additional level of uncertainty due to limited evidence on *Straticyte*^{TM} (13). Additionally, the collective uncertainty of all of the parameters serves to generate uncertainty at the decision making level. Hence, the net monetary benefit (NMB) approach was used to characterize the decision uncertainty and results presented in a cost-effectiveness acceptability curve (CEAC) (13).

RESULTS

Base Case Analysis

The incorporation of *Straticyte*^{TM} into the current prognostic algorithm (i.e. histopathology) was cost saving as it led to a slightly lower per patient cost and fewer cancer cases over a five-year time horizon compared to histopathology alone ($ 3,360 versus $ 3,553, and 31 versus 36 per 100

patients, respectively) (Table 2). The histopathology and *Straticyte*^{TM} prognostic algorithm was determined to be the dominant strategy (more effective and less costly).

Exploratory Scenario Analyses

Given that *Straticyte*^{TM} is not in the market place yet and its indication is not finalized, its cost-effectiveness was assessed when it was only applied to moderate and mild cases (scenario #1) (Table 3). The incorporation of *Straticyte*^{TM} remained the dominant strategy in scenario #1 ($ 3,192 versus $ 3,551, and 28 cancer cases versus 35 cancer cases per 100 patients *Straticyte*^{TM} and histopathology versus histopathology alone, respectively). However, when *Straticyte*^{TM} was only used for cancer cases (i.e. scenario #2), it no longer was the dominant strategy. Over a five-year time horizon, *Straticyte*^{TM} and histopathology was the more expensive approach albeit still more effective than histopathology alone for an ICER of $8,610/cancer cases avoided (Table 3).

Sensitivity Analyses

One-way sensitivity analysis (OWSA): In almost all cases explored in the OWSA, *Straticyte*^{TM} and histopathology was cost saving (more effective and cheaper) compared to histopathology alone. Changes in several parameters, such as the number of visits per year specifically, by applying only 2 visits per year (i.e. every 6 months instead of 3 to the moderate group in histopathology group), relative risk of malignant transformation and probability of developing cancer from mild dysplasia, were found to have meaningful impact on the model outcome. In all three of these cases, the incorporation of *Straticyte*^{TM} was associated with slightly higher costs but still better outcomes than histopathology alone.

Probabilistic Sensitivity Analysis (PSA): The CEAC was constructed using MC simulation to demonstrate decision uncertainty. In this study, the CEAC explored the probability of *Straticyte*^{TM}

and histopathology having the greatest net benefit compared to histopathology alone over a range of potential willingness to pay (WTP) thresholds (Figure 2). At the lowest WTP threshold, *Straticyte*^{TM} and histopathology was the more cost-effective strategy (89% of the simulations) than histopathology alone (11% of the stimulations). With higher thresholds, the probability in which *Straticyte*^{TM} and histopathology was the cost-effective option (i.e. the most attractive option) decreased slightly reaching a horizontal asymptote, whereby it offered the highest net benefit in 84% of the simulations (Figure 2).

DISCUSSION

Principal findings: In the base case analysis from the private payers and out-of-pocket perspectives, the algorithm of *Straticyte*^{TM} and histopathology dominated the current standard of care, by incurring lower cost and less cancer cases developed over five-years. Uncertainty was considered in this economic model through several sensitivity analyses, for which the results remained robust. The majority of incremental cost-effectiveness ratio (ICER) values obtained from all investigated parameters kept the algorithm with *Straticyte*^{TM} the dominant strategy, suggesting that it leads to better outcomes and is less expensive than current practices. The model parameters, number of visits per year, relative risk of malignant transformation (MT), and probability of developing cancer from mild dysplasia led to less cancer cases, though was slightly more expensive. However, the cost-difference was less than $10,000/QALY, which is substantially lower than the often presumed Canadian threshold of $100,000/QALY for the field of oncology, thus remains cost-effective. PSA allowed us to determine the overall impact of the model inputs on the outcome of interest. The result obtained from this analysis was very close to the base case analysis, where the algorithm with *Straticyte*^{TM} was the dominant approach. The CEAC curve generated from the MC simulation demonstrated that the algorithm with *Straticyte*^{TM} always had

a higher probability of being cost-effective. However, the curve illustrates that there is a slight gap in the available evidence to inform decision-makers to adopt the new technology, since it had less than 100% probability of being cost-effective at very high WTP thresholds. This is not surprising given that *Straticyte*^{TM} data is currently limited. As more information is gathered and estimates become more precise, they would progressively fill in this gap, allowing for continuous reassessment and strengthening of the economic output of the model.

Study in context of relevant literature: There have been no previous CEA of *Straticyte*^{TM} and literature on early CEA is limited. Recently, a few studies have presented general overview of methods to conduct early CEA and briefly applied suggested methods into the process of late CEA to demonstrate their potential usefulness in conducting early CEA (3, 5, 11, 14, 19-22). The literature highlights that integration of health economic modeling into early decision is not extensively practiced in pharmaceutical industry, and nearly absent for devices (23). In pharmaceutical companies, CEAs are mostly conducted for marketing and reimbursement purposes versus research and development, despite the fact that economic factors are usually considered the second leading cause for research termination of an early technology (24, 25).

Limitations and strengths: This early CEA is associated with several limitations. First, there is a paucity of high level clinical evidence regarding the effectiveness of *Straticyte*^{TM} , which is the nature of conducting any kind of analysis at a product's early stages of development (4). We attempted to account for this by conducting several sensitivity analyses to test our assumptions of effectiveness and clinical use. Second, methods used in this early economic analysis are vaguely described in the literature and are commonly only pilot studies (3, 11, 14, 19-22). Given the nature of this analysis, these methods can be conceptually challenging and rely highly on a number of assumptions (26, 27). This makes the results very susceptible to critique by experts in the field

pertaining to the technology, despite attempts to account for these assumptions through sensitivity analyses. To ensure clinical relevance, we sought expert advice throughout the evaluation process to help identify gaps and provide direction. Lastly, since some of the information such as the frequency of follow-ups was inputs by experts' opinion based on their everyday practice, stricter follow-up (3 months vs. 6 months) could potential be more effective over long-term in identifying new precancerous lesions, recurrences, which may have resulted in improved outcomes due to earlier treatment. Therefore, another major limitation of this study was not considering the potential additional benefits due to stricter follow-up by O&M surgeons. This paper has several strengths. First, we conducted an extensive review of the literature to identify methodologies of early CEA (Khoudigian et al, manuscript in preparation). Second, we sought clinical expert opinions as well as opinions of leaders in HTA to inform our analyses. Third, we are the first to incorporate multiple methods that were suggested and piloted in the literature to complete a thorough early CEA to determine the potential value of *Straticyte*^{TM}.

Implications for clinicians and policymakers: The considerable burden of disease and expense of oral cancer in Canada highlights the importance of accurately predicting the risk of developing oral cancer to both patients and the health care system (5). *Straticyte*^{TM}, is at its early premarket stage of its lifecycle, hence this was an attempt to compare the costs and outcomes of incorporating it to the current prognostic algorithm using limited data related to its clinical use and effectiveness. Decision analytical modeling techniques as well as qualitative methods, such as belief elicitation method and scenario drafting, were applied, and parameters for which the model outcome is most sensitive was explored. This provides a thorough early CEA that is important for clinicians and policymakers to consider. Furthermore, whilst presenting a successful attempt in early modeling and the difficulties associated with it, this paper creates a potential foundation to work on and build

a guiding framework in creating more robust early models, with useful insight into the potential value of the product at that moment as well as meet the requirements of fully developed models at late stages of the product's life cycle.

Unanswered questions and future research considerations: Canadian policy makers have to make informed decisions on how to allocate resources for the population in the most efficient manner, given increasing health expenditures and scarce resources (1). These decisions generally are based on both clinical and cost-effectiveness evidence of new health technologies compared with standard care or alternative technologies (1). Even though cost-effectiveness analysis within health technology assessment has long been recognized as a compelling way to ascertain value for buyers, its role in the allocation of research and development by companies is not well described. There is no set guideline that helps guide on how to conduct CEAs during the early stages of a technology's development life cycle and how to deal with challenges associated with the lack of both clinical and economic evidence. Despite the development in health economic methods to support reimbursement after the product is in the market place, the use of CEA at the early stages of product's development is less explored and needs further research.

Conclusion: This early CEA demonstrates a high probability of success that *Straticyte*^{TM} will be cost-effective. This supports continued investment by the manufacturer, and that investment by the healthcare system and individual patients may be worthwhile. Data is currently limited, and as the product cycle progresses, additional information will inform the model and provide more accurate estimates of the technology's cost effectiveness.

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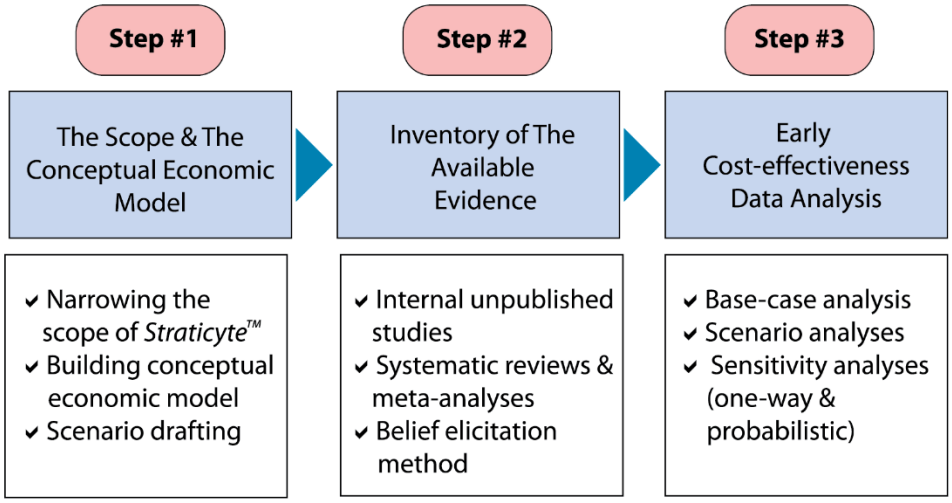


Figure 1: The Three Key Steps Followed to Conduct Early Cost-Effectiveness Analysis.

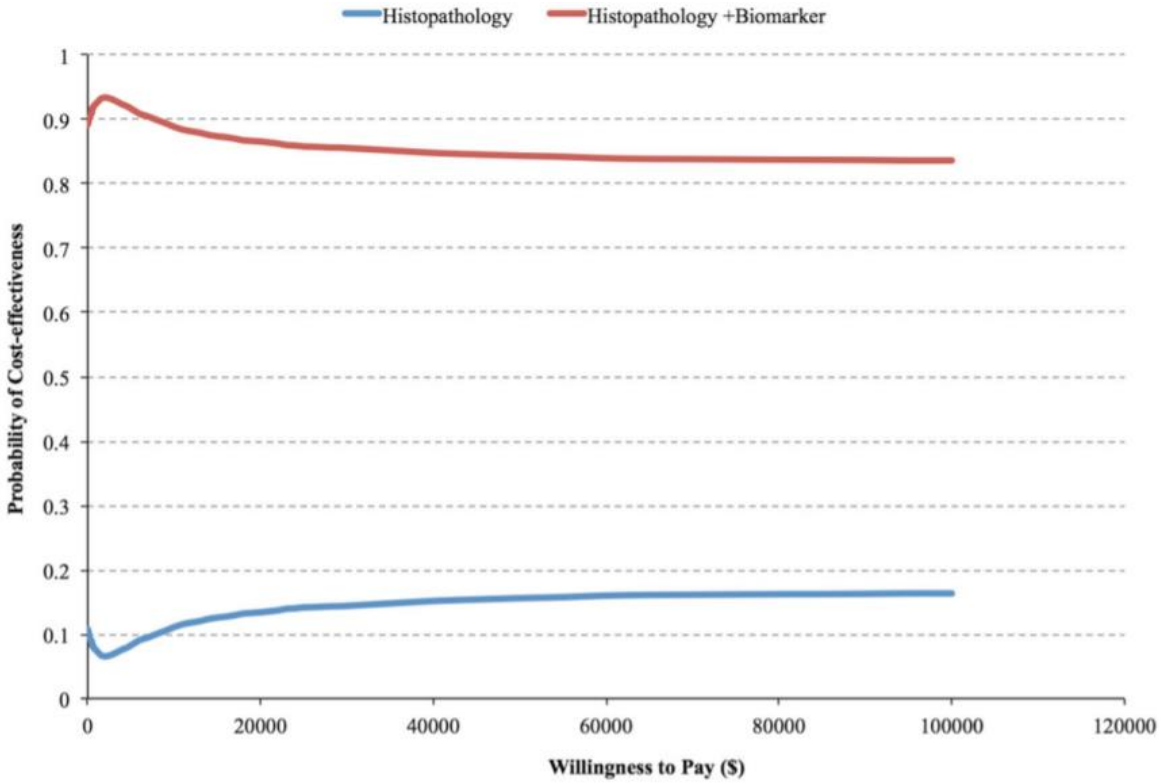


Figure 2: The Cost-Effectiveness Acceptability Curve of the Early-CEA of the New Prognostic Tool, *Straticyte*™. The Willingness to Pay Threshold is for Cancer Cases Avoided.

Table 1: The Model Input Parameters

Parameters$^{\Psi}$	Base case	Deterministic		Probabilistic	Reference/ Sources
		Low value	High value	Distribution	
Transition probabilities*					
pSevere	0.271	0.187	0.355	Dirichlet (α_1=29, α_2=78)	12
pModerate	0.355	0.264	0.446	Dirichlet (α_1=38, α_2=69)	12
pMild	0.374	0.282	0.466	Dirichlet (α_1=40, α_2=67)	12
pSevere_C	0.759	0.603	0.914	Beta (α=22, β=7)	12
pModerate_C	0.632	0.478	0.785	Beta (α=24, β=14)	12
pMild_C	0.375	0.225	0.525	Beta (α=15, β=25)	12
pSevere_HighR	0.931	0.839	1.023	Dirichlet (α_1=27, α_2=2)	12
pModerate_HighR	0.158	0.042	0.274	Dirichlet (α_1=6, α_2=32)	12
pMild_HighR	N/A	N/A	N/A	Dirichlet (α_1=0, α_2=40)	12
pSevere_MediumR	0.069	0.000	0.161	Dirichlet (α_1=2, α_2=27)	12
pModerate_MediumR	0.842	0.726	0.958	Dirichlet (α_1=32, α_2=6)	12
pMild_MediumR	0.500	0.345	0.655	Dirichlet (α_1=20, α_2=20)	12
pSevere_LowR	N/A	N/A	N/A	Dirichlet (α_1=0, α_2=29)	12
pModerate_LowR	N/A	N/A	N/A	Dirichlet (α_1=0, α_2=38)	12
pMild_LowR	0.500	0.345	0.655	Dirichlet (α_1=20, α_2=20)	12
pSevere_HighR_C	0.815	0.668	0.961	Beta (α=22, β=5)	12
pModerate_HighR_C	0.833	0.535	1.132	Beta (α=5, β=1)	12
pMild_HighR_C	N/A	N/A	N/A	Beta (α=0, β=0)	12
pSevere_MediumR_C	N/A	N/A	N/A	Beta (α=0, β=2)	12
pModerate_MediumR_C	0.594	0.424	0.764	Beta (α=19, β=13)	12
pMild_MediumR_C	0.550	0.332	0.768	Beta (α=11, β=9)	12
pSevere_LowR_C	N/A	N/A	N/A	Beta (α=0, β=0)	12
pModerate_LowR_C	N/A	N/A	N/A	Beta (α=0, β=0)	12
pMild_LowR_C	0.200	0.025	0.375	Beta (α=4, β=16)	12
Relative risk of developing cancer with Excision (i.e. surgery)					
rrMT	0.51	0.230	1.140	LogNormal [ln (mean = -0.673, SE=0.408]	SR/MA
Costs and Resources					
cHistopathology	$ 88	$ 70.4	$ 105.6	Gamma (α100=, β=0.88)	34
cBiomarker	$ 250	$ 200	$ 300	Gamma (α=100, β=2.5)	Manufacturer
cExcision	$ 384	$ 307.2	$ 460.8	Gamma (α=100, β=3.84)	34
cFollow-up	$ 129	$ 103.2	$ 154.8	Gamma (α=100, β=1.29)	34
cPathology	$ 95	$ 76	$ 114	Gamma (α=100, β=0.95)	Experts Opinion
cPainMed_T2	$ 12.65	$ 10.15	$ 15.15	Gamma (α=100, β=0.127)	Experts Opinion
cPainMed_P	$ 25.17	$ 22.67	$ 27.67	Gamma (α=100, β=0.252)	Experts Opinion
cWork_Loss	25.42	20.336	30.504	Gamma (α=100, β=0.254)	16
cTransportation	0.575	0.46	0.69	Gamma (α=100, β=0.00575)	16
cParking	20x	16x	24x	Gamma (α=100, β=0.2)	Assumption
HRSofWORK	24 hrs	0 hrs	40 hrs	Gamma (α=100, β=0.240)	Experts Opinion
avgDISTANCE	60 Km	48 Km	72 Km	Gamma (α=100, β=0.600)	Assumption
employed	0.9271	0	0	None	16
V_E6M_year	2 visits	1 visits	3 visits	None	Experts Opinion
V_E3M_year	4 visits	3 visits	5 visits	None	Experts Opinion

p= probability; C= cancer; x: times; R= risk; rrMT= relative risk of malignant transformation; c= cost; T2= Tylenol 2; p= peridex; V= visits; E6M= every 6 months; E3M= every 3 months; SR/MA= systematic review and meta-analysis; Beta= Beta distribution; Gamma= Gamma distribution; Dirichlet: Dirichlet distribution.

Table 2: The Incremental Cost-Effectiveness Results of the Base Case Analysis from the Private and Patient's Perspective and Time Horizon of 5-Years.

	Histopathology + *Stratictye*^{TM}	**Histopathology**
Total cost	$ 3,359.62	$ 3,553.28
Total cancer cases	0.31 (31 per 100 patient)	0.36 (36 per 100 patient)
Incremental cost	($ 194.36)	*Histopathology + Stratictye*^{TM} *DOMINATES Histopathology*
Cancer cases avoided	0.05	
ICER	Dominant	

ICER: Incremental cost effectiveness ratio

Table 3: The Incremental Cost-effectiveness Results of the Exploratory Scenarios from the Private and Patient's Perspective and Time Horizon of 5-Years.

(A) Scenario #1		
	Histopathology + *Stratictye*^{TM}	**Histopathology**
Total cost	$ 3,192	$ 3,550.69
Total cancer cases	0.28 (28 per 100 patient	0.35 (35 per 100 patient)
Incremental cost	($ 359)	*Histopathology + Stratictye*^{TM} *DOMINATES Histopathology*
Cancer cases avoided	0.07	
ICER	Dominates (cost saving)	
(B) Scenario #2		
	Histopathology + *Stratictye*^{TM}	**Histopathology**
Total cost	$ 2,605	$ 1,399.45
Total cancer cases	0.24 (24 per 100 patient)	0.38 (38 per 100 patient)
Incremental cost	($ 1,205)	
Cancer cases avoided	0.14	
ICER	$ 8,610/ cancer case avoided	

ICER: Incremental cost effectiveness ratio

Supplementary Material 3. I – Qualitative and Quantitative Approaches to Conduct Early Cost-Effectiveness Analysis for Medical Devices

A. Quantitative Approaches:
1. Scenario Drafting **2.** Belief Elicitation Method
B. Qualitative Approaches (mostly used for drugs):
1. Headroom Analysis **2.** Bayesian Analysis **3.** Value of Information Analysis

Supplementary Material 3. II – Defining the Scope of Early Cost-Effectiveness Model for Straticyte™

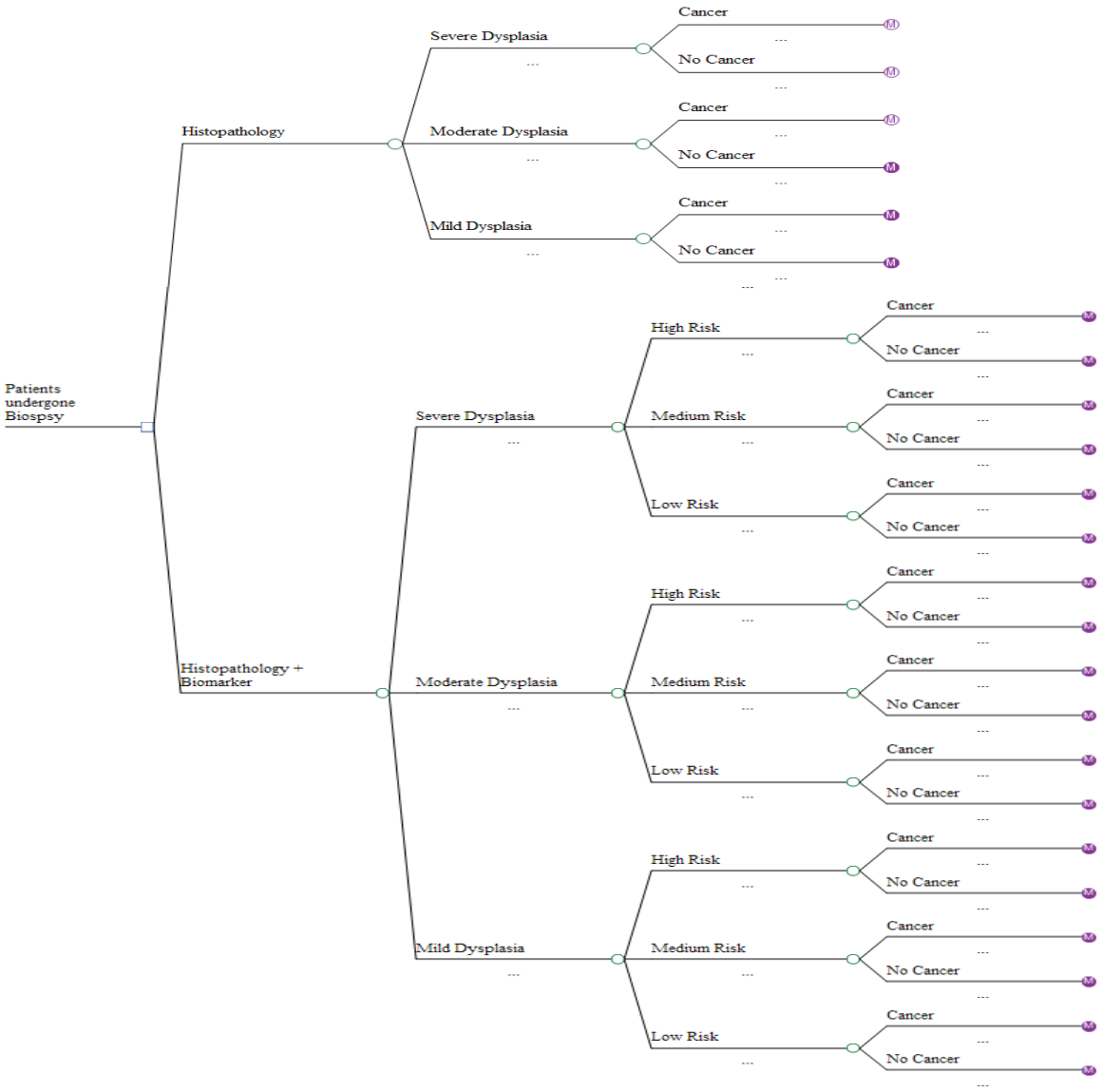
Application:	The application was using *"Straticyte™"* in the health-care system to predict the risk of developing oral cancer for patients with pre-malignant lesions
Population:	The target population was individuals 35 years of age and older and have undergone biopsy for suspected oral cancer
Comparator:	The comparator was the current prognostic test, histopathology (i.e. gold standard), applied by oral and maxillofacial (O&M) surgeons
Outcome:	The outcomes taken into account were effectiveness of *"Straticyte™"*, defined as cancer cases avoided, as well as the direct and indirect costs
Intervention:	The intervention was the new prognostic strategy, *"Starticyte™"*, in addition to Histopathology (i.e. gold standard)

Supplementary Material 3. III – Four Key Model Assumptions

1. Patients had dysplasia and were not treated and that the malignant transformation rate observed, reflects the natural disease progression.
1. Treatmeant decision depending on *Straticyte*™ + histopathology and histopathology alone were based on expert opinion.
3. The number of days off work (on average 3 days, ranges from 0 to 7 days) after excision was based on expert opinion.
4. The most common medications prescribed to patients who have undergone excision were Tylenol 2 and Peridex, which was based on expert opinion.

Supplementary Material 3. IV – Decision Analytic Model

Figure 1: The Decision Analytic Model for Oral Pre-cancerous Lesions. Patients who have already undergone biopsy are diagnosed either by histopathology, where the dysplasia is graded as severe, moderate or mild based on the extent of the architectural and cytological changes, or with histopathology and *Stratictye*^{TM}, where patients in each dysplasia grading are further classified as high, medium, or low risk of developing oral cancer based on the result of the *Stratictye*^{TM} test. These categorizations are mapped in mutually exclusive pathways.



Supplementary Material 3. V – The Literature Search Strategies

OVERVIEW	
Interface:	OVID
Databases:	MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)*1946 to Present*
Date of Search:	November 11th, 2014
Updated Search:	May 9th, 2016
Study Types:	Randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; case control studies; observational studies
Limits:	None

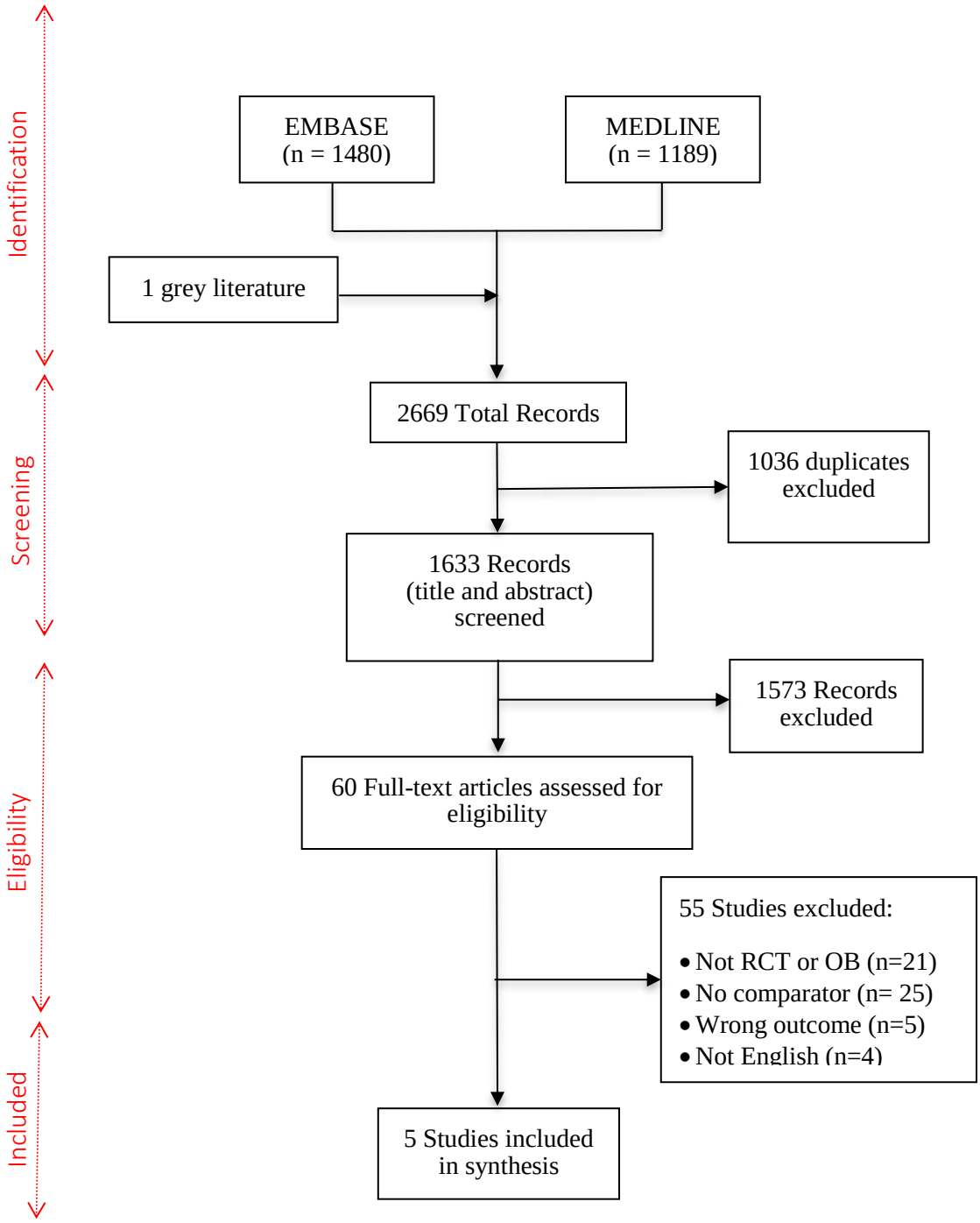
DATABASE STRATEGY	
Searches	**Results**
Dysplasia.mp	61545
Oral.mp	528729
1 or 2	2981
Mouth.mp	126950
1 or 4	1690
3 or 5	3274
(Progression or follow-up or follow up or treatment or cohort or natural history or recurrence).mp	4549690
6 and 7	1189

OVERVIEW	
Interface:	OVID
Databases:	EMBASE 1974 to 2014 November 06
Date of Search:	November 11th, 2014
Updated Search:	May 9th, 2016
Study Types:	Randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; case control studies; observational studies
Limits:	None

Database Strategy		
#	**Searches**	**Results**
1	Dysplasia.mp	92591
2	Oral.mp	905041

3	1 or 2	4304
4	Mouth.mp	195526
5	1 or 4	2664
6	3 or 5	5040
7	(Progression or follow-up or follow up or treatment or cohort or natural history or recurrence).mp	5792535
8	6 and 7	1480

Supplementary Material 3. VI – The PRISMA Flow Chart

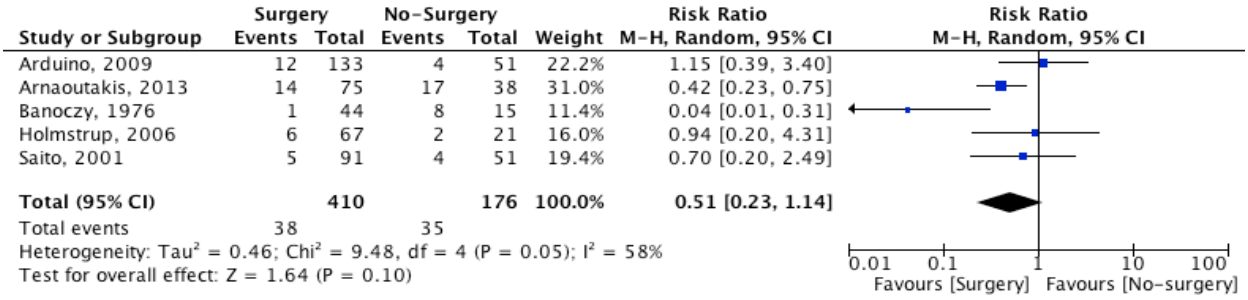


Supplementary Material 3. VII – The Characteristics of the Included Studies

Author, year	Country	Methodology/ setting	Date of enrollment	Mean age	# of cancer cases/ total # of surgically treated patients	# of cancer cases/ total # of non-surgically treated patients
Saito, 2001 [28]	Japan	Retrospective/ Hospital	1976-1997	54	5/91	4/51
Banoczy, 1976 [29]	Hungary	Retrospective/ Hospital	NR	NR	1/44	8/15
Arduino, 2009 [30]	Italy	Retrospective/ Hospital	1991-2007	63.58	12/133	3/74
Arnaoutakis, 2013 [31]	USA	Retrospective/ Hospital	1990-2011	59.2	14/75	4/51
Holmstrup, 2006 [32]	Denmark	Retrospective/ Pathology laboratory	1977-1997	60.8	6/67	2/21

Supplementary Material 3. VIII – The Forest Plot by RevMan

Brief description of how RR is estimated and used in this economic evaluation: The MTRs from the included studies were pooled and the RR of malignant transformation over 5 years was determined using the Cochrane Collaboration Review Manager analysis version 5.2 Statistical Software (RevMan 5.2). Following this, the outcome of elicitation (details found in the "Clinical practice by oral and maxillofacial (O&M) surgeons" section of the manuscript on pages 3-4 as well as Appendix Table 7) dictated where in the decision tree (i.e. which branch) the RR of developing oral cancer given excision and the associated costs and resources are applied.



Supplementary Material 3. IX – Questionnaire for Oral and Maxillofacial Surgeons

Date of interview: _____

Interviewer information

Name:

Interviewee Information

Name: _____

Occupation: _____

Address: _____

_____

Phone: _____

E-mail: _____

PROJECT TITLE: *The Premarket Assessment of the Cost-Effectiveness of a Predictive Technology "Straticyte™" for the Early Detection of Oral Cancer: A Decision Analytic Model*

PROJECT OVERVIEW:

Health economic evaluation provides information about the value for money of new healthcare technologies, and is increasingly used to guide the allocation of scarce resources based on maximizing health gain. The molecular diagnostics company, PDI, has developed a technology to improve the identification of patients at high risk for oral cancers for early intervention, and distinguish abnormal cell growth that will not become malignant, compared to the current gold standard alone. This more accurate diagnosis could save lives, reduce morbidity from traumatic surgeries, increase the duration of productive work lives, and save healthcare costs. The purpose of this internship is to develop a health economic model to evaluate the cost-effectiveness of the technology, as well as its social impact. The results of the model will help determine whether the new technology demonstrates economic value.

DEFINITIONS:

No risk factor: none

Moderate risk factor: Only smokes; Only Drinks; HPV/ RBV infected; Immune-compromised; HIV infected

High risk factor: Prior Cancer; more than one of these: smoker, alcoholic, HPV/RBV infected, Immune-compromised, HIV infected

QUESTIONNAIRS					
Prognostic tool		**Biomarker**	**Risk Factor**	**Treatment**	**Follow-up**
Histop	Severe Dysplasia	-	No Risk Factor		
		-	Moderate Risk Factor		
			High Risk Factor		

	Moderate Dysplasia	- -	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
	Mild Dysplasia	-	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
Histopathology + Biomarker	Severe Dysplasia	High Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
		Medium Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
		Low Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
	Moderate Dysplasia	High Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
		Medium Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
		Low Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
	Mild Dysplasia	High Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
		Medium Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		
		Low Risk	No Risk Factor		
			Moderate Risk Factor		
			High Risk Factor		

Supplementary Material 3. X – The Overall Result of the Questionnaires

	Treatment	**Follow-up**
Histopathology		
Severe Dysplasia	Local excision	Every 6 months for 5 years
Moderate Dysplasia	Local excision	Every 3 months for 5 years
Mild Dysplasia	Monitor	Every 6 months for 2 years
***Straticyte*™ and Histopathology**		
Severe Dysplasia + High Risk	Local excision	Every 6 months for 5 years
Severe Dysplasia + Medium Risk	Local excision	Every 6 months for 5 years
Severe Dysplasia + Low Risk	Local excision	Every 6 months for 5 years
Moderate Dysplasia + High Risk	Local excision	Every 6 months for 5 years
Moderate Dysplasia + Medium Risk	Local excision	Every 6 months for 5 years
Moderate Dysplasia + Low Risk	Local excision	Every 3 months for 5 years
Mild Dysplasia + High Risk	Local excision	Every 6 months for 5 years
Mild Dysplasia + Medium Risk	Local excision	Every 6 months for 5 years
Mild Dysplasia + Low Risk	Monitor	Every 6 months for 2 years

Supplementary Material 3. XI – Costing Details

Oral Biopsy Cost:	The excision, and cost of monitoring patients were estimated from the 2014 Ontario Dental Association (ODA) Suggested Fee Guide For Dental Services
Cost of Pathology	The technician and preparation of the pathology report, were obtained by interviewing a pathologist from the Mount Sinai Hospital – Pathology and Laboratory Medicine located in Toronto, Canada
Cost of *Straticyte*™	The cost of running the test, the technician cost, the cost of reporting the outcome of the test as well as the administrative costs for the O&M surgeon and the pathologist, was derived from Proteocyte Diagnostic Inc
Prescribed Drugs	*Tylenol 2*® to control pain and *Peridex*™ to treat gingivitis were taken into consideration in patients who have undergone excision

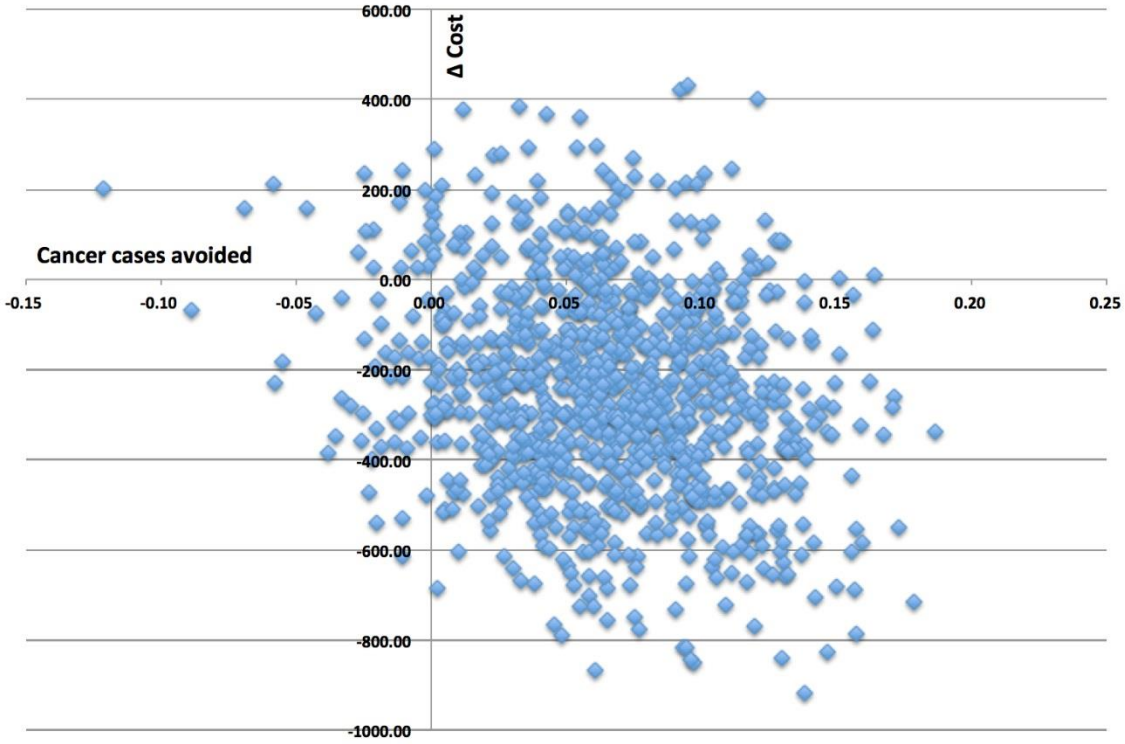
Supplementary Material 3. XII – Definitions of the Model Input Parameters

Parameters	Definitions
Transition Probabilities	
pSevere	*Probability of severe cases based on Histopathology over 5 years*
pModerate	*Probability of moderate cases based on Histopathology over 5 years*
pMild	*Probability of mild cases based on Histopathology over 5 years*
pSevere_C	*Probability of patients who developed cancer over 5 years who were diagnosed as severe cases based on Histopathology*
pModerate_C	*Probability of patients who developed cancer over 5 years who were diagnosed as moderate cases based on Histopathology*
pMild_C	*Probability of patients who developed cancer over 5 years who were diagnosed as mild cases based on Histopathology*
pSevere_HighR	*Probability of severe cases based on Histopathology and high risk prognosis with Starticyte™ over 5 years*
pModerate_HighR	*Probability of moderate cases based on Histopathology and high risk prognosis with Starticyte™ over 5 years*
pMild_HighR	*Probability of mild cases based on Histopathology and high risk prognosis with Starticyte™ over 5 years*
pSevere_MediumR	*Probability of severe cases based on Histopathology and medium risk prognosis with Starticyte™ over 5 years*
pModerate_MediumR	*Probability of moderate cases based on Histopathology and medium risk prognosis with Starticyte™ over 5 years*
pMild_MediumR	*Probability of mild cases based on Histopathology and medium risk prognosis with Starticyte™ over 5 years*
pSevere_LowR	*Probability of severe cases based on Histopathology and low risk prognosis with Starticyte™ over 5 years*
pModerate_LowR	*Probability of moderate cases based on Histopathology and low risk prognosis with Starticyte™ over 5 years*
pMild_LowR	*Probability of Mild cases based on Histopathology and low risk prognosis with Starticyte™ over 5 years*
pSevere_HighR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as severe cases based on Histopathology and high risk prognosis with Starticyte™*
pModerate_HighR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as moderate cases based on Histopathology and high risk prognosis with Starticyte™*
pMild_HighR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as mild cases based on Histopathology and high risk prognosis with Starticyte™*
pSevere_MediumR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as severe cases based on Histopathology and medium risk prognosis with Starticyte™*

pModerate_MediumR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as moderate cases based on Histopathology and medium risk prognosis with Starticyte™*
pMild_MediumR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as mild cases based on Histopathology and medium risk prognosis with Starticyte™*
pSevere_LowR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as severe cases based on Histopathology and low risk prognosis with Starticyte™*
pModerate_LowR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as moderate cases based on Histopathology and low risk prognosis with Starticyte™*
pMild_LowR_C	*Probability of patients who developed cancer over 5 years who were diagnosed as mild cases based on Histopathology and low risk prognosis with Starticyte™*
Malignant Transformation Rate (MTR)	
rrMT	*Relative risk of Malignant Transformation of oral lesions by treatment modality (surgical excision vs. no surgery)*
Costs and Resources	
cHistopathology	*Cost of Biopsy by incision ($73 + 20% higher since oral surgeons do it)*
cBiomarker	*Cost of Biomarker test based on Proteocyte Inc.*
cExcision	*Average cost of excision (≤1cm, 1-2cm, 2-3cm, 3-4cm, 4-6cm, 6-9cm, 9-15cm, ≥15cm)*
cMonitor	*Cost of monioring patients (per visit)*
cPathology	*Cost of technician & pathology report*
cPainMed_T2	*Cost of pain medication if prescribed after the excision (Surgery)*
cPainMed_P	*Cost of antiseptics if prescribed after the excision (Surgery)*
cWork_Loss	*Average hourly wage rate*
cTransportation	*Cost of transportation per km travelled by patients have to visit oral surgeon for monitoring*
cParking	*Cost of parking when patients have to visit oral surgeon for monitoring*
HRSofWORK	*Hours of days of work after the excision*
avgDISTANCE	*Average distance a patient has to travel to get to an Oral & Maxillofacial Clinic*
employed	*Probability of patients employed in Canada*
V_E6M_year	*Number of days they are monitored per year*
V_E3M_year	*Number of days they are monitored per year*

p= probability; C= cancer; R= risk; rrMT= relative risk of malignant transformation; c= cost; T2= Tylenol 2; p= peridex; V= visits; E6M= every 6 months; E3M= every 3 months.

Supplementary Material 3. XIII – The Scattered Plot of 5000 Monte Carlo Simulations



CHAPTER 4 -

The Long-Term Cost-Effectiveness of a Predictive Technology *"Straticyte™"* for the Early Detection of Oral Cancer on the Healthcare System Compared to Standard of Care: A Markov Model *

SHORT TITLE

Long-term Cost-effectiveness of a Predictive Technology "*Straticyte*TM"

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**Khoudigian-Sinani et al. The Long-Term Cost-Effectiveness of a Predictive Technology "Straticyte™" for the Early Detection of Oral Cancer on the Healthcare System Compared to Standard of Care: A Markov Mode. 2018. Journal of Dental Research: in submission.*

ABSTRACT

Introduction: Oral cancer encompasses cancers of the head and neck. The annual mortality rate is high since most are diagnosed at advanced stages. Oral cancer patients are extremely expensive to treat, and early detection is of great importance. This study conducts an economic evaluation to examine the long-term impact of the introduction of *Straticyte*™ to clinical practice in addition to histopathology, compared to histopathology alone.

Methods: A lifetime Markov model was constructed from a public payer perspective with annual Markov cycles. This model used the number of cancer cases and no-cancer cases from a previously published study that assessed the early-CEA of *Straticyte*™. This Markov model consisted of six health states. Sex specific subgroup analyses, scenario analyses, and both one-way (OWSA) and probabilistic sensitivity analyses (PSA) were conducted to investigate the robustness and uncertainty of the model outcomes.

Results: Compared to histopathology alone, *Straticyte*™ with histopathology led to cost-savings and better quality adjusted life years (QALYs) over a lifetime horizon for the healthcare system. Furthermore, females incurred more costs but higher QALYs than males. When treatment effect was taken into consideration, incorporation of *Straticyte*™ remained the dominant strategy. The OWSA and PSA demonstrated that incorporation of *Straticyte*™ would be cost-effective over the majority of parameters and willingness to pay values.

Conclusion: This study demonstrates the positive downstream impact of *Straticyte*™ on the healthcare system, therefore the usefulness of this technology for the early detection of oral cancer. Incorporation of a detailed treatment effect in these patients, and using data from a large population, can strengthen the evidence and provide a more comprehensive and holistic understanding of the long-term impact of *Straticyte*™.

INTRODUCTION

Oral cancer encompasses cancers of the head and neck, which arises from five primary sites: larynx, pharynx, oral cavity, salivary glands, and paranasal sinuses (1). Oral cancer progresses in a stepwise fashion, from normal to pre-malignant to invasive carcinoma, over a period of approximately 10 years (2). The annual incidence of oral cancer is 300,000 persons worldwide, with a 5-year mortality rate of about 50% worldwide (1; 3). The high mortality rate is because most oral cancers are diagnosed at advanced stages, with 67% to 77% of patients not seeking consultation until they experience persistent pain, which is a symptom of advanced cancer (4; 5). Among patients who survive, late-stage lesions are costly and difficult to treat, with high morbidity. In Canada, the average cost of the standard five-year treatment of oral cancer is $45,699 CAD (6). Earlier diagnosis could significantly lower the mortality rate and treatment costs, as demonstrated by a recent study that reported a 17% drop in mortality rate for localized cancers, with an associated savings of up to $50,000 (7; 8).

The current standard of care (SOC) to diagnose oral lesions is surgical biopsy sample selection and histopathology examination (9). Due to the subjectivity of histopathology, there is great inter- and intra-observer variation of the evaluation (dysplasia grades), due to variations in pathologists' expertise and a lack of consensus for the evaluation (9; 10). This, in turn, has led to a wide range of dysplasia grading, with considerable prognostic overlap (11; 12). This results in unclear guidance for clinicians on how to treat individuals with oral potential malignant or pre-malignant lesions (OPLs) (13).

Recently there has been a considerable effort to refine prognostic ranges to better identify high risk OLPs, such as the development of biomarker tests (14; 15). *Straticyte*^{TM}, a novel prognostic

tool for oral cancer, has been investigated and linked to neoplasia progression. In a recently published paper, using *Straticyte*™ resulted in more accurate classifications of lesions at risk of progression to cancer than histopathological dysplasia grading alone, over a follow-up of a 5-year time-horizon (16). Additionally, another published paper investigated the cost-effectiveness of this prognostic tool, which demonstrated that, compared to histopathology alone, *Straticyte*™ in combination with histopathology incurred lower costs and led to less cancer cases over a 5-year time horizon (17).

Given that oral cancers negatively impact patients' mortality, and quality of life (QoL) and are extremely expensive to treat, early detection with a more sensitive new prognostic tool could save lives, reduce morbidity with less traumatic surgeries, and increase the duration of productive work lives. The aim of this economic evaluation was to examine the long-term impact of the introduction of *Straticyte*™ to clinical practice, in addition to histopathology, on the cost, patients' outcomes, and cost-effectiveness compared to histopathology alone.

METHODS

Model Structure, Details and Assumptions

A lifetime Markov model was constructed using Microsoft® Excel 2011 to estimate the long-term effect of introducing *Straticyte*™ on the cost and health outcomes (defined as quality adjusted life years (QALYs), compared to the histopathology. This analysis was conducted from the public payer perspective over a lifetime horizon, with annual Markov cycles. Model inputs and structure were chosen based on published data, including real-world evidence and recommendations from best practice modeling guidelines (18-21). Furthermore, based on existing guidelines for the

economic evaluation of health technologies, both future costs and utilities that occur beyond one year were discounted at an annual rate of 1.5% (21).

This model used the number of cancer and non-cancer cases from a previously published paper (17) that examined the use of *Straticyte*™ in combination with histopathology versus histopathology alone (Table 1). The target population of this published short-term economic analysis was individuals aged 35 years or older with and without cancer cases at the end of the published 5-year short-term model (17). Therefore, individuals at the end of this 5-year short term model (i.e. aged 40 years) with and without cancer cases were introduced and followed in this long-term Markov model.

Figure 1 represents the long-term Markov model structure, which consists of three key health states typical for oncology: (1) Stable (i.e. no cancer), (2) Progressed (i.e. cancer) and (3) Death. However, given the complexity of oral cancer, to better reflect the disease pathway and to capture the appropriate cost, the increased risk of death and the gradual decline in quality of life as cancer further progresses, the "progressed (i.e. cancer)" health state was split into four separate mutually exclusive health states: (1) Cancer stage 1; (2) Cancer stage 2; (3) Cancer stage 3; and (4) Cancer stage 4.

Patients not diagnosed with cancer over the 5-year time-horizon from the short-term model entered the "non-cancer" health state. Based on different transition probabilities, they stayed in the non-cancer health state, died, or progressed to cancer stage 1. All patients were assumed to be monitored regularly during the course of follow-up, such that if they did progress to cancer, it is assumed that it was detected at the earliest stage (i.e. stage 1).

Patients who were diagnosed with cancer within 5-years from the short-term model entered the "cancer stage 1" health state. These patients were monitored regularly during the course of follow-up in the short-term model; hence it was assumed that their cancer was detected at the earliest stage (i.e. stage 1). Once patients entered the "cancer stage 1" health state, based on different transition probabilities, these patients progressed from one cancer stage to the next, stayed in the same cancer stage, or died during the annual cycles of the Markov model.

Furthermore, it was also assumed that the stage that the patient happens to be in a particular cycle effects the costs, mortality and utility values. Patients without cancer were assumed to have the same mortality rate as the general population. The mortality rate assigned to each cancer stage was sex and age specific, based on previously published literature (22). The impact of subsequent treatment of cancer progression was not modeled in the base-case analysis, it was only considered in scenario analyses.

Model Parameters

The model parameters in this economic evaluation included transition probabilities, utility values, and costs (Table 2). However, given the aim of this study, no treatment effect was incorporated in the base case analysis for those that were diagnosed with cancer in both histopathology and *Straticyte*™ and histopathology arms.

Parameters were obtained from a variety of publicly available data sources, such as grey literature, expert opinion and published studies. Studies were identified by a targeted literature search, using biomedical databases (MEDLINE, EMBASE) and Google Scholar, using search terms such as "oral cancer", "utility values", "economic burden", "healthcare resource use", "cost-effectiveness," and "mortality rates."

Survival data: Transition probabilities were obtained from a published study conducted by Speight et al, 2006 in UK, as there were no appropriate Canadian estimates in the literature. In this study, records from the Thames Cancer Registry, at the individual tumor level, were used to calculate the transition probabilities using survival analysis techniques (26). For each transition, the annual hazard ratios and their associated variances were calculated by assuming a parametric survival distribution, and using the records of 6,093 patients (62% male, mean age 65.43 years). Sex, age, and stage of cancer affect the probability of death, thus these transition probabilities were used as model inputs (27). Furthermore, patients were assumed to face the fifth annual probability of death until the end of their lifetime.

Modeling the cancer stage-progression over time: Estimates of clinical upstaging in oral cancer were also obtained from the Thames Cancer Registry study, as there were no appropriate Canadian estimates in the literature. The estimates were gathered from expert opinions, empirically derived using the trial roulette approach (28), which is a commonly used method in the oncology field (29). This method quantifies the uncertainty of the estimate, using a beta distribution, compared to obtaining a single value through consensus among clinicians.

Utility values: Health utility values are related to health related quality of life and were used in the calculations of QALYs. Health utility values associated with oral pre-cancer and cancer cases were obtained from Downer et al, 1997 (24). This study used standard gamble techniques and reported utility values for two different health states: (1) early cancer (stage 1 and 2); and (2) later cancer (stage 3 and 4). We did not identify studies reporting a utility estimate separately for all four stages of oral cancer, thus in the model the same utility value was assigned to patients with

cancer stages 1 and 2, and with cancer stages 3 and 4. To account for uncertainty for these model inputs, beta distributions were assigned to each of the two utility values for the probabilistic analysis.

Healthcare resource use and costs: Healthcare resource use (HCRU) and associated costs, depending on the health state patients are in, were derived from a published real-world population based study in Ontario by Oliveira et al, 2016 (6). This study was conducted by linking 394,092 cancer patients from the Ontario Cancer Registry (OCR) to treatment data from Cancer Care Ontario (CCO) and administrative health care databases at the institute for clinical and evaluation sciences (ICES).

In the Oliveira paper, the net costs, as well as the cost difference between patients and matched non-cancer control subjects, were estimated by different phases of care and the patients' sex. The included costs were those associated with cancer specific treatments, such as chemotherapy and radiation therapy administered in hospitals, and other resources, such as physician services (primary care physicians, specialists, other physicians), diagnostic tests and laboratory services, outpatient prescription drugs (for patients aged 65 years or older and/or those receiving social assistance), inpatient hospitalization, ambulatory care, other institution-based care, and home care (6).

The cost associated with the pre-diagnosis phase in the study was assumed to be the cost incurred by patients in the "non-cancer" health state in the current analysis. The costs associated with initial and continuing phases were assumed to be the costs incurred by "cancer stage 1" and "cancer stage 2" health states, and the cost associated with the terminal phase was assumed to be incurred by patients in "cancer stage 3" and "cancer stage 4" health states (Table 2). All costs were annualized

for the lifetime Markov model, and inflated to 2018 Canadian dollars using the healthcare component of the Consumer Price Index (CPI).

Data Analysis

Base-case analysis: To estimate the long-term effect of the biomarker on costs, mortality and QoL for patients during their lifetime, the base-case analysis was performed for individuals aged 40 years or older who were diagnosed with and without oral cancer at the end of their fifth year in the published short term model (17). In this economic evaluation, the incremental cost and incremental health effects,measured in QALYs gained, were combined to determine the incremental cost-utility ratio (ICUR).

$$ICUR = \frac{C_N - C_O}{U_N - U_O}$$

Where, "C" stands for cost, "U" stands for utility, "N" stands for new intervention (i.e. Starticyte™ use in combination with histopathology arm) and "O" stands for old intervention (i.e. histopathology alone).

Furthermore, ICUR is calculated and reported only if there is a trade-off between higher incremental cost and higher QALYs gained between Starticyte™ in combination with histopathology and histopathology alone. Whenever one of this strategies was determined to be both cheaper and more effective than the other, ICUR was not calculated instead the new strategy was reported to "dominate" the old strategy, or be "dominated" by the old strategy.

Subgroup analysis: Subgroup analyses were conducted to explore potential difference in the cost-effectiveness of the use of Starticyte™ use in combination with histopathology compared to histopathology alone among males and females were separately.

Scenario analysis: Several scenarios in addition to the base-case analysis were explored. Alternative efficacy assumptions of possible treatment effects were investigated, as a series between 0% to 20% reductions, for all cancer progression stages. This analysis sought to inform the additional positive effect that treatment can have on these patients, by demonstrating a more holistic picture of the potential long-term impact of Starticyte™.

Sensitivity analysis: One-way sensitivity analyses (OWSA) were conducted for all input variables to explore the uncertainty around parameters in the base-case analysis (Table 2), and to find the parameters with the largest impact on model outcomes. The 95% CI of the model inputs were used to estimate its impact of key parameters on the incremental cost-effectiveness ratio. When 95% CIs were not available, the base case values were increased and decreased by 20%. The mean value for each input ±20% was considered a reasonable range to evaluate a model parameter in the deterministic model, and a tornado diagram was created to demonstrate the impact of the top five key model drivers.

Furthermore, probabilistic sensitivity analysis (PSA) was also conducted to take into account the overall uncertainty from the combined variability of several factors. In PSA, model results are simulated multiple times with values for model variables randomly chosen each simulation based on specified distributions and parameters (see Table 2). In the current PSA model results were simulated 1000 times using Monte Carlo (MC) methods, (30). The collective uncertainty of all of the parameters serves to generate uncertainty at the decision-making level. The results of PSA are presented in a cost-effectiveness plane and their corresponding cost-effectiveness acceptability curve (CEAC) (30).

RESULTS

Base Case Analysis

The base-case results presented for the entire population aged 40 to 75+ years led to cost-savings for the healthcare system, and better QALYs for patients with oral cancer in the long-term. The result is summarized in Table 3. The base-case analysis demonstrated cost savings and better QALYs over a lifetime horizon, compared to the histopathology alone. Given the cancer cases from the previous published model, in this Markov model the Starticyte^{TM} arm, with fewer cancer cases, compared to the histopathology arm, with slightly more cancer cases, led to lower lifetime cost ($76,891 vs. $84,323), and better QALYs (19.09 QALY vs. 17.94 QALY).

Subgroup Analyses

Given the sex differences observed for oral cancer risk (27), the cost-effectiveness of males and females were examined separately and summarized in Table 4. Overall, females led to less cost-savings but higher quality of life than males over a lifetime horizon. As seen in Table 4, female patients incurred more cost in both arms compared to males ($89,494 vs. $64,288 in the *Starticyte^{TM}* + histopathology arm, and $96,740 vs. $71,905 in the histopathology arm) but had higher QALYs than males (19.90 QALY vs. 18.27 QALY in the *Starticyte*^{TM} + histopathology arm and 18.72 QALY vs. 17.17 QALY in the histopathology arm). *Straticyte*^{TM} was dominant for both males and females.

Scenario Analyses

The base-case analysis was to demonstrate the long-term impact of detecting OLPs given the use of a more accurate prognostic tool, without taking into consideration the treatment effect on this economic evaluation. However, since treatment plays a role in disease progression, exploratory

analyses in which the effect of treatment was accounted for was also conducted and summarized in Table 5. Overall, when a relative risk reduction in malignant progression rate was taken into consideration, the incorporation of *Straticyte*™ remained the dominant strategy, leading to more cost-savings and better QALYs in the long run, compared to the result of the base-case analysis.

Sensitivity Analyses

One-way sensitivity analysis (OWSA): OWSA demonstrated the impact of individual model parameters on the cost-effectiveness of *Straticyte*™. In almost all cases explored, the introduction of *Straticyte*™ for early detection of OLPs was found to be the dominant strategy, leading to cost savings and better health outcomes compared to histopathology alone. Changes in the proportion of cancer cases entering the long-term model from the previously published short-term model were found to have a meaningful impact on the model outcome. When the lower and upper intervals of the 95% CI of cancer cases reported were investigated, in both the short-term model for histopathology and *Straticyte*™ with histopathology arms, it was determined that the introduction of *Straticyte*™ led to lower incremental cost-savings compared to the base case for the healthcare system when the 4 less cancer cases (i.e. 27 vs. 31 cancer cases per 100 patients) were treated in the histopathology arm. Furthermore, it was also determined that the use of *Straticyte*™ no longer led to cost savings when 4 more cancer cases (i.e. 35 vs 31 cancer cases per 100 patients) were treated in the *Straticyte*™ and histopathology arm compared to histopathology arm, respectively (Figure 2).

Probabilistic sensitivity analysis (PSA): CEACs show the probability that each strategy is cost effective as a function of the willingness to pay for a QALY. CEACs, was constructed using MC simulation, demonstrated the probability of *Starticyte™* in combination with histopathology as

having the greatest long-term net benefit compared to histopathology alone, over a range of potential willingness to pay (WTP) thresholds. In all three cases (as seen in Figure 3) - male population, female population and the total population - *Starticyte*^{TM} in combination with histopathology was the more cost-effective strategy in 99% of the simulations than histopathology alone, in 1% of the simulations. With higher thresholds, the probability in which *Starticyte*^{TM} in combination with histopathology was the cost-effective option reached a horizontal asymptote, whereby it offered the highest net benefit in 99% of the simulations.

DISCUSSION

Oral cancer is a major health problem, and is costly and difficult to diagnosis and treat. Early diagnosis and prevention through better detection of pre-cancerous oral lesions is of great interest, since it could significantly lower the morbidity and mortality rates, and reduce the costs associated with cancer care in Canada.

Principle Findings

The long-term impact of *Straticyte*^{TM}, in combination with histopathology, on the healthcare system for the detection of OPLs was the dominant strategy; it led to both lower long-term costs and better outcomes (QALYs) compared to histopathology alone. The more accurate the classification of lesions at risk of progression to cancer is, the more efficient the treatments will be (16). As seen in the previously published short-term model of *Straticyte*^{TM}, accurate detection of OLPs leads to less cancer cases over a 5-year follow-up period (17). As such, fewer cancer cases will automatically incur less healthcare costs over their lifetime.

Uncertainty in this model was investigated through OWSA and PSA, for which the results remained robust. In nearly all sensitivity analyses and scenarios, *Straticyte*^{TM}, in combination with

histopathology remained the dominant strategy for the healthcare system. The only parameter cost-effectiveness was sensitive to was changes in the proportion of cancer cases entering the long-term model, where an increase in the number of cancer cases in the *Straticyte*™ plus histopathology arm no longer led to cost-saving to the healthcare system. PSA was used to determine the overall impact of the model-inputs on the outcome of interest. The results from PSA were very similar to the base-case analyses, where the algorithm with *Straticyte*™ was the cost-saving approach. The CEAC curve generated from the MC simulation demonstrated that the algorithm with *Straticyte*™ always had a higher probability of being cost-effective. However, based on current evidence there is still some uncertainty on whether *Straticyte*™ in combination with histopathology is cost-effective., since it had less than 100% probability of being cost-effective at very high WTP thresholds. *Straticyte*™ in combination with histopathology had the same probability of not being cost effectives at all levels of WTP ≥ $0 according to the CEAC. Therefore not just at higher WTP thresholds. This indicated that *Straticyte*™ in combination with histopathology was dominated by histopathology alone in a small number of simulations, which were the cases where *Straticyte*™ in combination with histopathology had more cancer cases developed than histopathology alone. This was unsurprising, given that *Straticyte*™ data is currently limited and the short-term economic evaluation was an early cost-effectiveness analysis (17).

The long-term cost savings observed in this study was the downstream effect of cancer prevention through better pre-cancerous lesion detection from *Straticyte*™. Once developed the natural progression of cancer was incorporated in the model, however the impact of cancer treatment was not. Through exploratory/scenario analyses, further cost-savings were also observed when treatment effects - 10% and 20% risk reductions in malignant progression – were incorporated. This could be due to the fact that if cancer patients start doing better while on therapy, they will

on average use even less healthcare resources, and hence less associated healthcare costs. Based on current guidelines, testing of OLPs for early oral cancer detection is in the context of dental care, which is not publically funded in Canada, while cancer treatment is publically funded. Implementing a public funding strategy for a technology used in dental care in order to reduce costs for medical care may be challenging but of great benefit over long-term for decision makers.

Limitations and Strengths

This economic evaluation has several limitations. First, *Straticyte*™ data was based on an early CEA study, hence the paucity of high-level clinical evidence regarding the effectiveness of the new prognostic tool (31). Second, we did not identify any economic evaluations of prognostic tools for detecting OPLs, limiting our ability to compare inputs and findings to other published studies. Lastly, since the treatment effect was not included in the base-case analysis, patients' disease progression history may have been better, mortality might have been delayed in real-life, and the incremental QoL would have been less favorable. We attempted to account for this by conducting several scenario analyses to investigate the potential impact that the treatment effect has on the model outputs.

This paper has several strengths. First, we followed patients from the previous short-term early-CEA model to investigate the potential long-term impact of Starticyte™. Second, given the novelty of our work, we sought opinions from leaders in HTA to inform our analysis.

Conclusion and Further Research

This economic evaluation demonstrates the long-term impact of using Starticyte™ for detecting OPLs on the Canadian healthcare system. Starticyte™ in addition to standard of care results in more accurate detection of the risk of progressing to oral cancer, which ultimately leads to fewer

cancer cases, resulting better QoL among patients over a lifetime horizon, and cost-savings to the healthcare system.

The positive downstream effect supports the importance of early detection of oral cancer. Currently, *Straticyte*™ is either covered by private insurers or paid out of pocket, which limits access to patients who may benefit from early detection. This paper highlights the considerable cost-effectiveness to the public healthcare system over the long-term when payers invest in preventative technologies in dentistry that have downstream effects on cancer care.

Future research evaluating the impact of early detection of OPLs, while taking into consideration the public payers investment in *Straticyte*™ on a larger population, as well as detailed treatment effect in these patients, could help provide a more comprehensive and holistic understanding of the long-term impact of Starticyte™ for key stakeholders.

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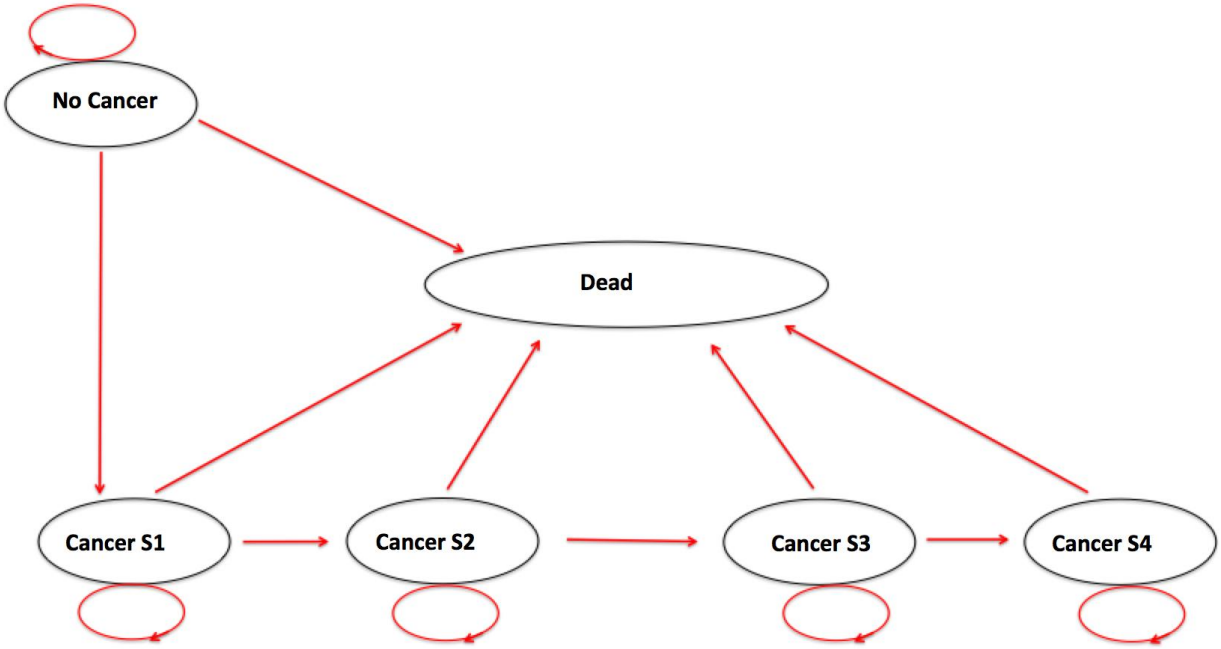

Figure 1: Overview of the Markov Model Showing the Six Health States: (i) No Cancer, (ii) Cancer Stage 1, (iii) Cancer Stage 2, (iv) Cancer Stage 3, (v) Cancer Stage 4 and (vi) Death

Table 1: The Proportion of Cancer and Non-Cancer Cases from Published Short-Term Model.

	Histopathology + *Straticyte*™	**Histopathology**
Proportion of cancer cases *(95% CI);* *beta distribution*	31 per 100 patients; (0.27,0.35); Beta distribution (α=159, b=354)	36 per 100 patients; (0.34, 0.38); Beta distribution (α=796, b=1,416)
Proportion of non-cancer cases *(1-cancer cases)*	69 per 100 patients	64 per 100 patients

Table 2: The Model Input Parameters.

Transition Probabilities	Base-case	Deterministic		Probabilistic	Sources/ References
		Low value (Mean - 20%)	High value (Mean + 20%)		
Probability of death in stage I (male): 40-49	0.085	0.068	0.102	Beta (α=27, b=293)	22
Probability of death in stage I (male): 50-59	0.104	0.083	0.125	Beta (α=33, b=287)	22
Probability of death in stage I (male): 60-69	0.120	0.096	0.144	Beta (α=38, b=282)	22
Probability of death in stage I (male): 70-79	0.173	0.138	0.208	Beta (α=55, b=265)	22
Probability of death in stage I (male): 80	0.261	0.209	0.313	Beta (α=84, b=236)	22
Probability of death in stage I (female): 40-49	0.071	0.056	0.085	Beta (α=16, b=207)	22
Probability of death in stage I (female): 50-59	0.086	0.069	0.104	Beta (α=19, b=203)	22
Probability of death in stage I (female): 60-69	0.099	0.079	0.119	Beta (α=22, b=200)	22
Probability of death in stage I (female): 70-79	0.143	0.115	0.172	Beta (α=32, b=191)	22
Probability of death in stage I (female): 80	0.216	0.173	0.259	Beta (α=48, b=174)	22
Probability of death in stage II (male): 40-49	0.146	0.117	0.175	Beta (α=27, b=160)	22
Probability of death in stage II (male): 50-59	0.179	0.143	0.215	Beta (α=34, b=154)	22
Probability of death in stage II (male): 60-69	0.205	0.164	0.246	Beta (α=39, b=149)	22
Probability of death in stage II (male): 70-79	0.297	0.237	0.356	Beta (α=56, b=132)	22
Probability of death in stage II (male): 80	0.447	0.358	0.537	Beta (α=84, b=104)	22
Probability of death in stage II (female): 40-49	0.121	0.097	0.145	Beta (α=12, b=89)	22
Probability of death in stage II (female): 50-59	0.148	0.118	0.177	Beta (α=15, b=86)	22
Probability of death in stage II (female): 60-69	0.170	0.136	0.204	Beta (α=17, b=84)	22
Probability of death in stage II (female): 70-79	0.360	0.288	0.432	Beta (α=36, b=65)	22
Probability of death in stage II (female): 80	0.370	0.296	0.444	Beta (α=37, b=64)	22
Probability of death in stage III (male): 40-49	0.172	0.138	0.207	Beta (α=34, b=162)	22
Probability of death in stage III (male): 50-59	0.211	0.169	0.253	Beta (α=41, b=155)	22
Probability of death in stage III (male): 60-69	0.242	0.193	0.290	Beta (α=47, b=148)	22
Probability of death in stage III (male): 70-79	0.350	0.280	0.420	Beta (α=68, b=127)	22
Probability of death in stage III (male): 80	0.527	0.422	0.633	Beta (α=103, b=93)	22
Probability of death in stage III (female): 40-49	0.143	0.114	0.171	Beta (α=15, b=90)	22
Probability of death in stage III (female): 50-59	0.174	0.139	0.209	Beta (α=18, b=87)	22
Probability of death in stage III (female): 60-69	0.200	0.160	0.240	Beta (α=21, b=84)	22
Probability of death in stage III (female): 70-79	0.289	0.231	0.347	Beta (α=30, b=75)	22
Probability of death in stage III (female): 80	0.436	0.349	0.524	Beta (α=46, b=59)	22
Probability of death in stage IV (male): 40-49	0.239	0.191	0.287	Beta (α=13, b=43)	22
Probability of death in stage IV (male): 50-59	0.292	0.234	0.351	Beta (α=16, b=40)	22
Probability of death in stage IV (male): 60-69	0.336	0.268	0.403	Beta (α=19, b=37)	22
Probability of death in stage IV (male): 70-79	0.485	0.388	0.582	Beta (α=27, b=29)	22

Probability of death in stage IV (male): 80	0.690	0.552	0.828	Beta (α=39, b=17)	22
Probability of death in stage IV (female): 40-49	0.198	0.158	0.237	Beta (α=6, b=24)	22
Probability of death in stage IV (female): 50-59	0.242	0.194	0.290	Beta (α=7, b=23)	22
Probability of death in stage IV (female): 60-69	0.278	0.222	0.333	Beta (α=8, b=22)	22
Probability of death in stage IV (female): 70-79	0.401	0.321	0.482	Beta (α=12, b=18)	22
Probability of death in stage IV (female): 80	0.605	0.484	0.726	Beta (α=18, b=12)	22
Probability of stage I to stage II	0.530	0.424	0.954	Beta (α=1.34, b=1.17)	22
Probability of stage II to III	0.590	0.472	1.062	Beta (α=1.67, b=1.17)	22
Probability of stage III to IV	0.670	0.536	1.206	Beta (α=1.67, b=1.17)	22
Probability of no cancer to stage I (male)	0.00017	0.00014	0.00021	-	23
Probability of no cancer to stage I (female)	0.00007	0.00006	0.00009	-	23
Utilities	**Base-case**	**Deterministic**		**Probabilistic**	**Sources/ References**
		Low value (95%CI)	**High value (95%CI)**		
Utility of no cancer	1	-	-	-	Assumption
Utility of cancer stage I & II	0.880	0.841	0.919	Beta (α=231, b=32)	24
Utility of cancer stage III & IV	0.680	0.615	0.745	Beta (α=135, b=64)	24
Utility of males: 40-44	0.910	-	-	-	25
Utility of males: 45-54	0.850	-	-	-	25
Utility of males: 55-64	0.800	-	-	-	25
Utility of males: 65-74	0.780	-	-	-	25
Utility of males: 75+	0.730	-	-	-	25
Utility of females: 40-44	0.910	-	-	-	25
Utility of females: 45-54	0.850	-	-	-	25
Utility of females: 55-64	0.810	-	-	-	25
Utility of females: 65-74	0.780	-	-	-	25
Utility of females: 75+	0.710	-	-	-	25
Costs & Resources	**Base-case**	**Deterministic**		**Probabilistic**	**Sources/ References**
		Low value (95%CI)	**High value (95%CI)**		
Cost of no cancer (male)	668	366	971	Gamma (α=17, b=38)	6
Cost of stage 1 part 1 (male)	22,127	22,115	22,141	Gamma (α=12,323,878, b=0)	6
Cost of stage 1 part 2 (male)	2,893	2,888	2,897	Gamma (α=1,592,631, b=0)	6
Cost of stage 2 part 1 (male)	22,127	22,115	22,141	Gamma (α=12,323878, b=0)	6
Cost of stage 2 part 2 (male)	2,893	2,888	2,897	Gamma (α=1,592,631, b=0)	6
Cost of stage 3 (male)	41,943	41,928	41,959	Gamma (α=27,336,585, b=0)	6
Cost of stage 4 (male)	41,943	41,928	41,959	Gamma (α=27,336,585, b=0)	6
Cost of no cancer (female)	1,367	985	1,749	Gamma (α=49, b=28)	6
Cost of stage 1 part 1 (female)	22,734	22,700	22,766	Gamma (α=1,748,946, b=0)	6

Cost of stage 1 part 2 (female)	3,958	3,949	3,967	Gamma (α=660,495, b=0)	6
Cost of stage 2 part 1 (female)	22,734	22,700	22,766	Gamma (α=1,748,946, b=0)	6
Cost of stage 2 part 2 (female)	3,958	3,949	3,967	Gamma (α=660,495, b=0)	6
Cost of stage 3 (female)	40,861	40,837	40,883	Gamma (α=11,530,462, b=0)	6
Cost of stage 4 (female)	40,861	40,837	40,883	Gamma (α=11,530,462, b=0)	6

Table 3: The Incremental Cost-Effectiveness Results of the Base Case Analysis from the Public Payer Perspective and Lifetime Horizon

	Histopathology + *Straticyte*™	**Histopathology**
Total cost	$76,891	$84,323
Total QALY	19.09	17.94
Incremental cost	($7,432)	
Incremental QALY	1.14	
ICUR	**Dominant**	

QALY: Quality adjusted life year; ICUR: Incremental cost utility ratio

Table 4: The Incremental Cost-Effectiveness Results of the Subgroup Analyses from the Public Payer Perspective and Lifetime Horizon

(A) Male Population		
	Histopathology + *Straticyte*™	**Histopathology**
Total cost	$64,288	$71,905
Total QALY	18.27	17.17
Incremental cost	($7,617)	Histopathology + *Straticyte*™ DOMINATES Histopathology
Incremental QALY	1.10	
ICUR	**Dominant**	
(B) Female Population		
	Histopathology + *Straticyte*™	**Histopathology**
Total cost	$89,494	$96,740
Total QALY	19.90	18.72
Incremental cost	($7,247)	Histopathology + *Straticyte*™ DOMINATES Histopathology
Incremental QALY	1.19	
ICUR	**Dominant**	

QALY: Quality adjusted life year; ICUR: Incremental cost utility ratio

Table 5: The Incremental Cost-Effectiveness Results of the Scenario Analyses from the Public Payer Perspective and Lifetime Horizon

(A) Treatment effect of 10% reduction in all stages		
	Histopathology + *Straticyte*™	**Histopathology**
Total cost	$77,364	$84,893
Total QALY	19.12	17.98
Incremental cost	($7,530)	Histopathology + *Straticyte*™ DOMINATES Histopathology
Incremental QALY	1.14	
ICUR	**Dominant**	
(B) Treatment effect of 20% reduction in all stages		
	Histopathology + *Straticyte*™	**Histopathology**
Total cost	$77,904	$85,545
Total QALY	19.17	18.03
Incremental cost	($7,641)	Histopathology + *Straticyte*™ DOMINATES Histopathology
Incremental QALY	1.13	
ICUR	**Dominant**	

QALY: Quality adjusted life year; ICUR: Incremental cost utility ratio

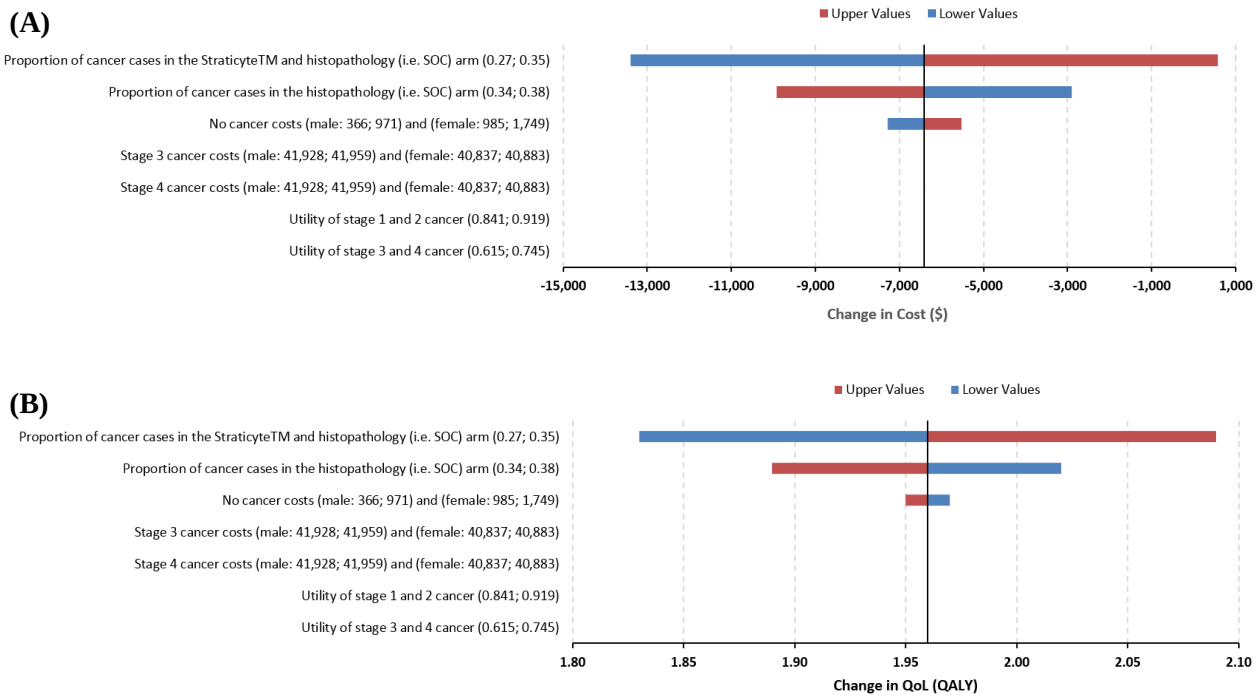

Figure 2: One-Way Sensitivity Analysis Demonstrating the Impact of Adjusting Individual Model Parameters on the Cost-Effectiveness of the *Straticyte*™ in Combination with Histopathology: (A) Change in Cost and (B) Change in Outcome (i.e. Quality Adjusted Life Year).

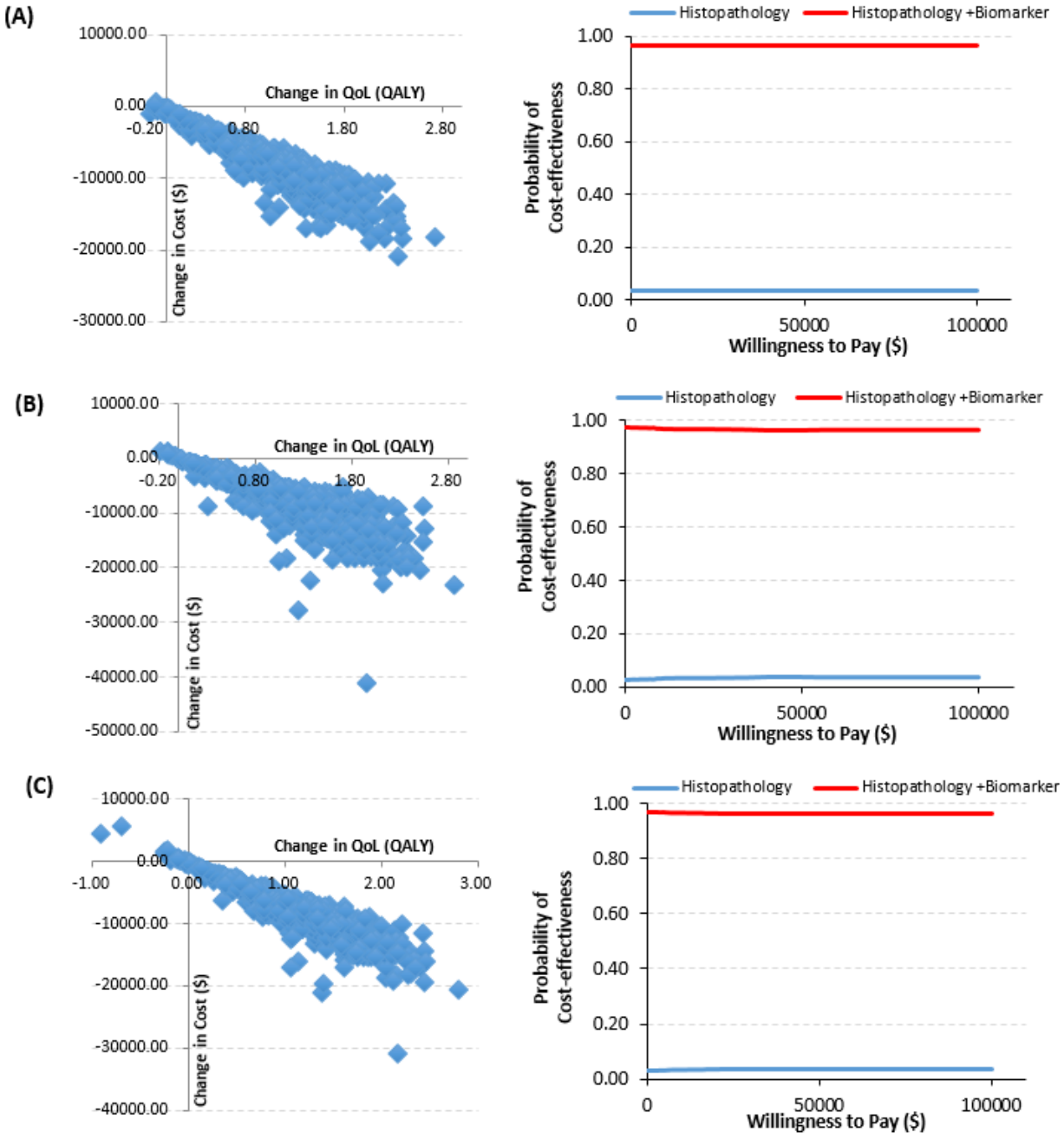

Figure 3: The Scattered Plots and the Associated Cost-Effectiveness Acceptability Curve of the Long-Term Economic Evaluation of the Use of Starticyte™ in Combination with Histopathology in Earlier Stages for the Detection of OPLs. Net Monetary Benefit is Used to Determine which Treatment was Cost-Effective for Each Simulation at Different Willingness to Pay Thresholds (WTPs) for QALYs Gained. (A) Male Population, (B) Female Population, (C) General Population.

CHAPTER 5 - Discussion and Conclusions of the Thesis

Summary and Major Contributions

There are a number of characteristics that are associated with medical devices that make them more challenging to assess than drugs. In most instances, there is limited evidence available about the clinical efficacy of medical devices and as a result, carrying out a cost-effectiveness analysis presents many challenges and is often not done. However, without evidence of cost-effectiveness, health care reimbursement agencies cannot make an informed decision about the value for money of any investments they wish to make. Furthermore, device manufacturers can use economic evaluation as a tool to make go, no-go decisions as well as secure market access. As a result, the objectives of this PhD thesis were twofold: 1) to systematically review the published literature of methods used to evaluated medical devices and to develop a framework to help guide the conduct of the economic evaluation of medical devices; and, 2) to determine the short-term and long-term cost-effectiveness of a novel prognostic tool for the early detection of oral cancer, *Straticyte*™.

Each chapter in this thesis was aimed at investigating the application of economic evaluation methods to medical devices. The inquiry addressed this topic from both a theoretical standpoint through the development of a framework and an empirical perspective by applying various methods to the evaluation of a novel medical device. This final chapter offers a summary of the thesis findings and the main contributions of each study, and of the overall thesis, in addressing the question on how to conduct economic evaluation of medical devices. It is further accompanied by a discussion of the implications of the results, some limitations and potential areas of future research.

The first chapter is a systematic literature review of the available methods for conducting economic evaluation of medical devices (Chapter 2). This review, which used a broad range of bibliographic resources with no limitations of language, resulted in the identification of a variety of methods used, or proposed for use, in the evaluation of medical devices. In addition, through appraising the available methods, key general stages of conducting CEA with limited evidence were generated, and methods were grouped into these stages. The output from this was the foundation for developing the conceptual guiding framework on CEA methodology for medical devices. The significance of this framework is that it provides HTA practitioners guidance to create economic models for medical devices. Additionally, the framework classifies and harmonizes the available methods, supporting the utilization of CEAs among key stakeholders for medical device development and implementation.

The second chapter applied the appropriate methods identified in the systematic literature review to estimate the cost-effectiveness of the introduction of a new prognostic tool, Starticyte^{TM}, to the standard of care for the detection of early oral cancer, from the private and patients' perspectives (Chapter 3). The results of the evaluation demonstrated high probability that this new prognostic tool will be a cost-effective approach in clinical practice, which as a result encourages continued investment in the product and possible reimbursement. The output of this was a successful application of CEA modeling, and highlighted the usefulness of the conceptual guiding framework on CEA methodology developed in the earlier Chapter. Further, the analysis emphasized the importance of a thorough CEA for clinicians and policy makers, since a robust early model could provide useful insights into the potential value of the product at the present moment, as well as help meet requirements of fully developed models at later stages of products life cycle.

The third chapter of this thesis used the output from the short-term cost-effectiveness model as the starting point of a lifetime Markov model (Chapter 4). The output of this economic evaluation demonstrated the potential long-term cost-savings of using *Straticyte*™, in combination with the current standard of care, for detecting early oral cancers on the Canadian healthcare system. The identification of the possible beneficial downstream effect on the healthcare system was possible because of successfully conducting the CEA using the methods identified in Chapter 2. Furthermore, this chapter highlighted the cost-effectiveness of *Straticyte*™ to the public healthcare system over the long-term when payers invest in preventative technology in dentistry, which has downstream effects on publically funded cancer care. This helps alert decision makers of upcoming innovations and provides preliminary evidence of the consequences of their adoption, which allows decision makers to incorporate the value and economic properties of an innovation, making resource allocation more efficient and optimize budgeting. Specific to this thesis, demonstration of the importance of a public funding strategy for a technology used in dental care in order to reduce costs for medical care, and lead to benefit over the long-term for decision makers.

Decisions on coverage and adoption of medical devices in healthcare systems are difficult for a number of reasons. For example, the effectiveness and health outcome is related to the proficiency and skill of the operator of the device. In addition, medical devices are constantly being modified which impact clinical efficacy/effectiveness and costs (1). This causes challenges, as the clinical evidence that is produced becomes no longer relevant as the device becomes obsolete with each iteration as well as changing prices (2). Even if incremental innovation is not an issue, there is often limited clinical evidence available due to the current regulatory requirements for market entry (3). However, increased interest in the economic evaluation of medical devices, for example

the Medical Technologies Evaluation Programme (4) in the UK, holds promise for improvements in the evaluation medical devices and improved decision-making by reimbursement agencies. The conceptual guiding framework for conducting CEA for medical devices developed in this thesis classifies and harmonizes the available methods, to support the utilization of CEA for key stakeholders in medical device development and implementation/adoption (5; 6).

Additional application of early-CEAs of medical devices, using the proposed conceptual guiding framework, would help identify the potential cost-effectiveness of novel medical devices in manufacturers' pipelines. Further, this could allow HTA practitioners to create registries of assessed medical devices, to be used to support further research and policy. This may also potentially enhance the transparency about the value for money for upcoming non-drug health technologies (i.e. medical devices), reduce the information asymmetry between drugs and devices prevalent in the market, and could also help shape the reimbursement landscape of medical devices.

The proposed conceptual guiding framework may have a significant impact on the reimbursement landscape by informing decision-making, from both the device manufacturer and the payer perspectives (7). From the manufacturer perspective, CEA maybe used for early market assessment, managing research and development portfolios, and informing the pricing and reimbursement scenarios (8; 9). These practices may help with the value proposition of the device to potential payers, and as a result improve chances of widespread implementation in clinical practice (8; 9). From the reimbursement perspective, decision-makers may benefit from the early exposure to the potential cost-effectiveness of the technology. This may facilitate the decision-making process, such as through incorporating the value and economic properties of an innovation

into current decision-making, forecasting, and anticipation of future technological development (7; 8; 9).

Limitations and Future Research

A limitation of the conceptual framework is that we only searched for early HTA methodologies used for medical device CEA, thus we may have missed potentially useful methodologies that may be applicable in later stages. Another limitation is that this framework has only been applied to the new technology explored in this thesis, *Straticyte™*, the generalizability of the ease and usefulness of the framework to other devices is unknown. Additionally, the framework does not take into account the organizational implications of adopting a medical device and the costs associated with any change management that may be required to implement the device. For the early CEA of *Straticyte™,* a limitation is that the methods used in this early CEA are vaguely described in the literature and are commonly only pilot studies, thus can be conceptually challenging and rely highly on a number of assumptions, leading to results that have considerable uncertainty. Furthermore, since the long-term economic model is informed by the short-term model, there is additional uncertainty in the final conclusion pertaining to the long-term effect of *Straticyte™*.

From a methodological point of view, analytical and pragmatic validations of this guiding framework are necessary. Analytical validation will help improve the framework by allowing subject-matter experts to judge its content and structure, while pragmatic validation will help assess and improve its feasibility and applicability by using the framework to conduct early-CEAs for different medical devices. Furthermore, future investment on the effectiveness of *Straticyte™* will strengthen the clinical effect and as a result will inform the health economic model and provide

more accurate cost-effectiveness estimate of *Straticyte*^{TM}. Consequently, it will also provide more robust understanding of the long-term impact of *Starticyte*^{TM} for key stakeholders.

We hope the output of this PhD thesis will trigger more interest around HTA assessment of medical devices, more specifically to help enable additional methodological advancements in assessing the clinical and economic aspect of medical devices, and validate and build upon the conceptual guiding framework for the economic evaluation of medical devices methodology. Over longer term, this may lead to the development of a common system and process specifically for medical devices, in a similar manner to pharmaceuticals, where key stakeholders bridge research and decision-making.

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