CADTH

HEALTH TECHNOLOGY ASSESSMENT REPORT

Composite Resin Versus Amalgam for Dental Restorations: A Health Technology Assessment

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Kelsey Seal contributed to study selection, data abstraction, and critical appraisal of included studies.

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Dr. Carlos Quiñonez contributed to the conception and design of the study and to the preparation and review of the draft report.

Monika Mierzwinski-Urban designed and executed the database search strategies for all the sections of the health technology assessment (HTA), completed grey literature searches, maintained search alerts, and prepared the search methods and appendices.

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Charlotte Wells contributed to the study selection, data abstraction, and revisions of the draft report.

Environmental Impact

Dr. Niladru Basu was the main researcher and author of the Environmental Impact chapter of the report.

Ethics

Dr. Daryl Pullman researched and composed the Ethics section of the report.

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Conflicts of Interest

Dr. Niladru Basu received funding/honorariums for writing a chapter concerning human exposure to mercury for the World Health Organization.

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Abbreviations

AMSTAR	Assessing the Methodological Quality of Systematic Reviews
BPA	bisphenol A
BPA-GMA	bisphenol A glycidyl methacrylate
CADTH	Canadian Agency for Drugs and Technnologies in Health
CI	confidence interval
ELSI	ethical, legal, and social issues
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hg	mercury
JBI-QARI	Joanna Briggs Institute-Qualitative Assessment and Review Instrument
HTA	health technology assessment
NECAT	New England Children's Amalgam Trial
NR	not reported
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RR	risk ratio
SD	standard deviation
SE	standard error
SR	systematic review
UNEP	United Nations Environment Programme
USPHS	United States Public Health Service
VAS	visual analogue scale
WHO	World Health Organization

Protocol Amendments

Section	Amendment	Page
Clinical	The calculation of kappa statistics was limited to the full-text phase of screening only because of the inclusive procedure for title and abstract screening (which rendered any citation deemed eligible by either reviewer to be included for full-text scrutiny), thus precluding the calculation of agreement for these citations.	17
Clinical	Data abstraction was completed using Microsoft Word tables as opposed to the protocol-specified application, DistillerSR. This was deemed to be a more efficient approach.	18
Clinical	Additional data for the review of safety were abstracted in accordance with adherence to the PRISMA-Harms checklist and extension paper.[1]	18-19

Executive Summary

Issue

Amalgam is a restorative material that has been widely used to treat dental caries for more than 150 years. But because dental amalgam is partly composed of mercury (Hg), its use has fuelled concern for decades about risks to human health. Composite resin is the most common alternative to dental amalgam; although data indicate that rates of restoration failure and secondary caries — as well as costs — are higher compared with amalgam. As well, the potential for toxicity to human health from composite resin restorations vis-à-vis compounds such as bisphenol A, for instance, remain uncertain.

Given longstanding debate around the use of dental amalgam, alongside a global impetus to phase down its use, a comprehensive evaluation of its benefits, harms, and other consequences is necessary to inform Canadian decision-makers. Specifically, this health technology assessment (HTA) sought to inform the following policy question:

Should dental amalgam continue to be used in Canada?

Objectives and Research Questions

This HTA aims to inform the policy question through a comparative assessment of dental amalgam and composite resin restorations, including investigation into the efficacy, safety, cost-consequence, patient perspectives and experiences, implementation issues, environmental impact, and ethical considerations.

Clinical Review

1. What is the comparative efficacy of direct dental restorations made of composite resin versus amalgam for the treatment of dental caries in permanent posterior teeth?
2. What is the comparative safety of dental restorations made of composite resin versus amalgam in children and adults?

Economic Review

3. What are the comparative consequences and costs of using dental restorations made of composite resin or amalgam for permanent teeth in Canada?

Patient Perspectives and Experience

4. What are the perspectives and experiences of patients (adults or children), parents of children patients, or caregivers around dental amalgam and composite resin restorations?

Implementation Issues

5. What is the current use of amalgam restorations in Canadian dental practices or programs?
6. What is the current use of composite resin restorations in Canadian dental practices or programs?

7. What factors influence the use of amalgam or composite resin restorations in Canadian dental practices or programs?

Environmental Assessment

8. What are the environmental effects associated with the use of dental amalgams versus composite resin restorations?

Ethics

9. What are the ethical issues associated with the use of dental amalgams compared with the use of composite resin restorations?

Clinical Review

Method

To address the question concerning the efficacy of dental amalgam as compared with composite resin restorations, a 2014 Cochrane systematic review (SR) was updated because of its consistency in objective and scope with those of the clinical review. Electronic databases and grey literature sources were searched for studies published since the search was completed for the original SR; i.e., retrieval was limited to studies published since January 2012. Eligible studies were randomized controlled trials (RCTs) describing a comparison between dental amalgam and composite resin restorations in carious, posterior, permanent teeth, and reporting on efficacy outcomes, including restoration failure, secondary caries, and restoration fracture.

The question concerning safety was addressed using a *de novo* SR. Electronic databases and grey literature sources were searched for studies from database inception for those addressing amalgam, and from January, 2006 for those addressing composite resin, in order to account for the development of composite resin as a dental material across time, and the consequent lesser relevance of older studies. Eligible studies were those reporting on primary research of dental caries patients of any age comparing dental amalgam and composite resin restorations and reporting on outcomes of relevance to safety and/or harms, including toxicity, sensitivity, allergy and/or injury.

For both clinical reviews, two independent reviewers screened titles and abstracts, as well as full-text articles in duplicate. One researcher abstracted data from included studies and a second researcher verified these data. The risk of bias of included RCTs was assessed using the Cochrane Risk of Bias Tool, which was applied by two independent assessors.

Findings

One eligible RCT was found for the update to the 2014 Cochrane SR; i.e., a 2016 split-mouth RCT of 40 teeth (in 20 patients) conducted in Turkey. Because of methodological and clinical heterogeneity between the 2016 study and those included in the primary meta-analyses of the original SR, a quantitative synthesis incorporating data from the 2016 RCT was not deemed to be feasible. While the 2014 Cochrane SR reported primary meta-analyses of two RCTs including 3,010 teeth, and indicating a significantly higher risk of restoration failure and secondary caries in composite resin as compared with amalgam, the 2016 RCT identified in the update reported no difference between composite resin and amalgam in restoration failure or secondary caries. Notably, the sample size in the 2016 study was considerably smaller than those included in the primary meta-analyses of the 2014 Cochrane SR.

The *de novo* review of safety identified 10 eligible study reports addressing safety outcomes — all of which were reports of RCTs — including the one study identified in the 2014 Cochrane SR update, which addressed post-operative sensitivity. The other nine were reports of toxicity outcomes measured in the two trials that comprised the primary meta-analysis for the 2014 Cochrane SR updated in question 1. No included studies addressed allergy or injury outcomes. Significantly higher urinary Hg levels were reported in amalgam patients in two trials through to five and six years of follow-up, respectively — although no measurements approached levels known to be toxic at any point in time. Notably, unadjusted urinary Hg levels at seven years follow-up in one of these trials were found to no longer differ significantly between treatment groups ($P = 0.07$), suggesting that mercury exposure from dental amalgam restorations may attenuate across time. Reports describing renal effects, physical development, and neuropsychological and psychosocial outcomes found few statistically significant differences between groups for most outcomes, with some subscale differences identified that variably favoured either the composite resin or amalgam groups, resulting in no discernible effect pattern. Finally, no statistically significant differences were observed between treatment groups in evaluations of neurological symptoms and immune function.

The risk of bias assessments identified at least some risk of bias in all of the included studies: In particular, because neither study participants nor clinicians placing the dental restorations could be blinded to the type of restoration that was placed, the risk of performance bias was deemed to be high in all of the included studies.

Economic Evaluation

Method

A cost-consequence analysis was conducted to evaluate the comparative consequences and costs associated with composite resin and amalgam as restorative materials for permanent, posterior teeth, within a Canadian societal perspective. Based on available data, four of seven consequences were selected as part of the economic evaluation: useful life of a restoration, lifetime need for restoration replacement, annual mercury waste management, and patient productivity loss associated with undergoing dental restoration.

Findings

Assuming a two- or three-surface restoration, on average, the useful life of an amalgam restoration for a permanent posterior tooth was longer compared with a composite resin restoration (amalgam: 132.6 months versus composite: 95.7 months) and costs less (amalgam: $171 versus composite: $219). Time-to-failure was longer for amalgam restorations, resulting in a lifetime cost that was estimated to be half that of composite resin restorations when assuming that a failed restoration would be replaced by another of the same size and of the same material. This was one of the simplifying assumptions required for the lifetime analysis because of a lack of data on the natural history following a failed restoration. As such, different scenario analyses were conducted that considered dental extraction or crown procedure after multiple restoration failures. Costs were found to be similar between the two groups, although composite resin restoration resulted in a younger age at which crowns or tooth extractions would be performed. In Canada, the annual cost of amalgam separators to manage mercury waste was estimated to be more than $16 million, but their use has ensured that dentistry's contribution to Canada's mercury burden in surface waters is negligible. Finally, it was estimated that a composite resin restoration would require several additional minutes for placement compared to an amalgam

restoration, and this would generate an incremental productivity loss for patients of less than $2 per restoration.

Patient Perspectives and Experiences

Method

A literature search of electronic databases and grey literature sources was conducted. Citations and full-text articles were screened by two independent reviewers. Eligible studies were primary, English-language, qualitative and mixed-methods studies, with separate reporting of a qualitative component and participant voice data that addressed the review question. Qualitative papers selected for retrieval were assessed by two independent reviewers for methodological quality using the JBI Qualitative Assessment and Review Instrument (JBI-QARI). Both descriptive study data and study results were extracted from papers included in the review by two independent reviewers and data were meta-synthesized to produce a single comprehensive set of synthesized findings that can be used as a basis for evidence-based practice.

Findings

Five papers describing four studies were identified as eligible for the review. Overall, the quality of the studies was assessed as being high. All four included studies focused on patients' health complaints and symptoms that they attributed to their dental amalgam restorations. No studies were located that addressed patients' experiences with composite resin restorations. Through a focus on patients with amalgam restorations and their experiences of perceived adverse reactions to the amalgam, this review highlights their struggle to be understood and believed as they searched for a cause for their sense of ill health.

Implementation Issues

Method

To understand the current context and implementation issues associated with the use of dental amalgams and composite resin fillings in Canadian dental care settings, telephone consultations and a review of the published literature were conducted. The literature search was performed by an information specialist, using a peer-reviewed search strategy. Eligible reports were English- and French-language sources that described implementation and context issues, including barriers and facilitators, associated with the use of dental amalgams and composite resins in dental care settings in Canada. Article selection and data extraction were completed by one reviewer. A narrative summary of the findings was undertaken. Interviews were conducted with targeted experts and stakeholders identified through the clinician networks managed by CADTH to provide a general overview of policy, funding, practice, and issues related to using dental amalgams and composite resins in dental care settings in Canada.

Findings

Nine eligible articles were identified and five stakeholders representing a variety of sectors in Canadian dentistry were consulted. Relevant information from the literature and the stakeholder consultations as it relates to each of the INTEGRATE-HTA context and implementation domains follows. The findings best fit within the following INTEGRATE-HTA framework's implementation and context domains of "policy," "funding/cost," "organization and structure," "provider," and "sociocultural." A variety of factors influence the use of one

type of restorative material over another. These include funding and reimbursement, the dental provider setting (public or private), provider attitudes and perceptions, provider education and training, patient perceptions, education and preferences, and sociocultural attitudes toward dental restoration materials. It is expected that dental providers educate patients about the most appropriate choice of restoration for their clinical case, but patients may make choices based on a variety of reasons, such as what materials are reimbursed and are available in their area, aesthetic concerns, health concerns, and what is recommended by their dentist. Ultimately, each individual case and patient are different, which means these factors can both act as barriers or facilitators to the use of different restoration materials in Canada.

Environmental Assessment

Method

A literature search of electronic databases and grey literature sources was conducted to inform a comparative assessment of potential environmental effects associated with the use of dental amalgams versus composite resins. One reviewer screened and selected reports that provided insight into the potential environmental impact associated with dental amalgam and composite resin restorations. Data were abstracted from each relevant article, including information related to the environmental impact. For both amalgam and composite resin, we then categorized the data into key risk assessment criteria — namely hazard identification, exposure assessment, and toxicology — and summarized the findings narratively.

Findings

The literature review identified 19 eligible articles. Given the available data of the relevance to the environmental impact, a detailed comparison of dental composite resins and amalgams was not possible. Whereas mercury has been established as a chemical that is persistent, bioaccumulative, and toxic, the relative small contribution of mercury into the Canadian ecosystem from its use in dentistry, as well as the over-time declines in its use, suggest that the potential impact on the environment is much less than from other sources. There is an increasing use of composite materials such as dental fillings, although relatively little is known about most of these chemicals and, in particular, their fate in the environment and downstream impacts on the ecosystem. Most of the attention and information available is on bisphenol A and, whereas this chemical has been shown to contaminate ecosystems and disrupt fish and wildlife health, linking potential impacts back to the Canadian dental sector is not possible with the current state of knowledge.

Ethical Considerations

Method

A literature search of electronic databases and grey literature sources was conducted. Additional relevant literature was also found using less systematic searching of both indexed and grey literature sources. Citations and full-text articles were screened by a single reviewer. Eligible articles included English-language publications providing a normative analysis of ethical issues arising in the use of amalgams or resins, presenting empirical research directly addressing an ethical issue arising from the use of amalgams or resins, or explicitly identifying but not analyzing or empirically investigating ethical issues arising from the use of amalgams or resins. Any identification of an issue by the public, patients, health care providers, researchers, or policy-makers was of interest whether or not

it was presented through rigorous ethical argumentation. Literature was not excluded based on methodological rigour. The analysis drew most directly on two classic perspectives, namely the utilitarian/consequentialist approach, and the deontological/duty-based approach. Other ethical perspectives, such as virtue theory, also informed elements of the analysis.

Findings

The ethics analysis identified a range of issues which can broadly be divided into macro, meso, and micro concerns. Macro-level considerations include ensuring compliance with environmental regulation and directives regarding the appropriate handling of amalgam waste, as well as appropriate funding policies and research to continue to develop quality dental restoration materials. At the meso level, there are questions regarding potential conflicts of interest and financial incentives for selecting one material over another. Additionally, the need for clear communication to patients about the nature of the materials and corresponding benefit or risks was identified. Public health education and clear communication are related to the micro level consideration of informed consent when using restorations. Additional micro level considerations include the right for dentists to refuse to provide services they believe to be harmful to patients, and ensuring patients are treated with respect, particularly those who explore possible connections between their restoration materials and chronic health issues.

Conclusions

The best available evidence indicates that, compared with composite resin, amalgam restorations appear to be more clinically efficacious and as safe, while also costing less. In addition, dental amalgam waste constitutes a small relative contribution to overall mercury contamination in the Canadian environment compared with other sources — largely owing to the judicious management of resultant mercury waste. Given these considerations, there is no clear reason to discontinue the use of dental amalgam in Canada.

Nevertheless, there is a global effort to phase down the use of dental amalgam, and composite resin materials undergo continual development and improvement. At the individual dental practice level, providers may choose to offer patients only one type of material for a number of reasons; among those who choose to provide both, however, there is a real opportunity for them to engage in discussion and shared decision-making with patients to balance the desirable and undesirable consequences of using either type of restorative material.

Introduction

Dental caries is a significant oral health problem worldwide.[2] While the epidemiology of dental caries across time and populations has changed — because of such factors as economic development, sugar consumption, and community water fluoridation — it remains an important cause of human morbidity, including pain, tooth loss, and downstream sequelae (e.g., school or work absenteeism) that negatively affect the activities of daily life.[3] In Canada, data collected between 2007 and 2009 indicate that 57% of children aged six to 11 years, 59% of adolescents aged 12 to 19 years, and 96% of adults have a history of dental caries.[4]

Standard treatment for dental caries aims to restore the structure of the affected tooth using filling material to replace decayed dental tissue.[5] Amalgam fillings have been widely used for more than 150 years.[6] Some factors supporting the widespread and enduring use of amalgam as a dental restorative material include its strength, durability, and low cost.[7-9]

While elemental mercury and dental amalgam are not synonymous, because amalgam is partly composed of mercury, concerns have been raised across time regarding both the environmental and health impacts of dental amalgam. Mercury is designated as a toxic substance under the *Canadian Environmental Protection Act, 1999*.[10] The placement or removal of amalgam fillings produces amalgam debris, which can be introduced into the environment through waste water from dental offices.[11] While waste management initiatives and requirements introduced in recent years for Canadian dental facilities have contributed to a significant reduction of amalgam waste discharge into the environment,[12] on the international front, the United Nations Environment Programme has established the *Minamata Convention on Mercury*, which aims "to protect the human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds."[13] In addition to the use of mercury in general, the *Minamata Convention* addresses the use of amalgam in dentistry by recommending a phase-down of its use; specifically, parties who have ratified the *Convention* commit to the adoption of at least two of nine proposed measures.[13] The *Convention* entered into force internationally on August 16, 2017;[14] and as of February 1, 2018, it had been ratified by 88 governments worldwide.[15] Canada signed the *Minamata Convention* in 2013,[16] ratified it in April 2017,[17] and has established measures to ensure compliance with the *Convention*'s requirements to phase down the use of dental amalgam.[18] Nonetheless, an important concern arising from the proposed phasing down of dental amalgam is the impact on the cost of dental care — which is known to be a barrier for some disadvantaged groups in Canada.[4,9]

In addition to concerns regarding the environmental impact of mercury, concerns have persisted over its safety for human health.[19] The surface(s) of dental amalgam fillings are known to release very small amounts of mercury vapour, particularly when stimulated by regular activities such as brushing teeth, chewing, eating hot foods and liquids, and grinding of the teeth.[9,19,20] Similarly, the placement and removal of amalgam fillings exposes patients and dental personnel to low levels of mercury vapour.[20] Depending on the level of exposure, mercury can cause significant adverse health effects, including neurological and kidney diseases.[19] For instance, evidence has shown that urinary mercury values of 7 mcg/L pose little risk to human health, whereas values of 25 mcg/L indicate an increased risk of adverse health effects, and values of 50mcg/L or greater may result in the onset of sub-clinical and clinical symptoms of mercury poisoning.[9] While these potential harms have raised concern, current evidence suggests that the levels of mercury exposure from dental amalgam fillings are unlikely to pose a serious risk to human health.[9]

Among the alternatives to the use of amalgam as a restorative material for dental caries, composite resin is the most common, having been in use for more than 50 years (although experience with newer iterations of composite resin would be shorter).[21] Throughout that time, composite resin materials have undergone considerable development and improvements — making them a viable alternative for direct dental restoration.[22] Initially limited to restorations in anterior teeth, modern composite resin, with its improved formulations and capacity to withstand stress and wear, has been used more commonly in posterior teeth instead of amalgam.[23] A distinct advantage of composite resin is that it can be colour-matched to the tooth being restored, giving it an aesthetic advantage over the silver, metallic colour of amalgam — a feature that has increased patient demand for dental restorations made of composite resin.[7,24] However, rates of restoration failure and secondary caries in composite resin restorations have been shown to be higher than those in amalgam restorations.[6] Further, the placement of restorations made of composite resin involves a more demanding, time-consuming procedure than that of restorations made of amalgam.[7,24] As with other procedures, the clinician's technique is considered an important factor in the placement of restorations made of composite resin — more so than for those made of amalgam — and may affect the quality, longevity, and outcomes achieved.[24] Evidence also suggests that restorations made of composite resin have a higher initial cost compared with those made of amalgam.[25] Similarly, the long-term costs associated with composite resin have been found to exceed those of amalgam; mostly owing to the shorter median survival time of composite resin restorations and the consequent need for more frequent repair and/or replacement.[25]

Concerns have also been raised about the safety of composite resin restorations because of the potential toxicity of some composite resin materials that may contain derivatives of bisphenol A (BPA), such as "…bisphenol A diglycidyl methacrylate (bis-GMA) especially, but also bisphenol A dimethacrylate (bis-DMA), polycarbonate-modified bis-GMA (PC bis-GMA), ethoxylated bisphenol A glycol dimethacrylate (bis-EMA) and 2,2-bis [(4-methacryloxy polyethoxy) phenyl]propane (bis-MPEPP)]."[26] However, similar to mercury and amalgam, composite resin is not synonymous with the materials used to manufacture it. In 2010, the World Health Organization (WHO) concluded that an unsafe level of exposure to BPA in humans could not be determined given available data, but that dental materials were unlikely to be an important source of exposure to BPA as compared to that from plastic food and drink containers, primarily.[27] A more recent publication from the European Food Safety Authority aligns with the WHO assessment of BPA exposure from dental materials; it further concludes that, relative to others, dental materials (including composite resin restorations, among others) are not an important source of chronic exposure, and as such that they were not considered in the European Food Safety Authority's exposure estimates.[28] These exposure estimates were used to establish a recommended temporary total daily intake of no more than 4 mcg/kg body weight — a threshold that exceeds estimated average daily exposure levels.[28]

Given the global impetus to address environmental and health concerns posed by mercury in general, and the phase-down of dental amalgam in particular, a comprehensive evaluation of the benefits, harms, and other consequences of dental restorations made of amalgam compared with the primary alternative restoration material (composite resin) is needed to inform Canadian decision-makers.

Policy Question

Should dental amalgam continue to be used in Canada?

Analytic Framework

The analytic framework informing this Health Technology Assessment (HTA) is presented in Appendix 1.

Objectives

The objective of this HTA is to inform the policy question through a comparative assessment of dental amalgam and the most commonly used alternative in Canada; i.e., composite resin. Specifically, the HTA aims to address the comparative efficacy, longevity and safety, cost-consequence, patient perspectives and experience, ethical and implementation issues, and the environmental impact of dental restorations made of amalgam versus composite resin for the treatment of dental caries.

Research Questions

The HTA addresses the following research questions:

Clinical Review

1. What is the comparative efficacy of direct dental restorations made of composite resin versus amalgam for the treatment of dental caries in permanent posterior teeth?
2. What is the comparative safety of dental restorations made of composite resin versus amalgam in children and adults?

Economic Review

3. What are the comparative consequences and costs of using dental restorations made of composite resin or amalgam for permanent teeth in Canada?

Patient Perspectives and Experience

4. What are the perspectives and experiences of patients (adults or children), parents of children patients, or caregivers around dental amalgam and composite resin restorations?

Implementation Issues

5. What is the current use of amalgam restorations in Canadian dental practices or programs?
6. What is the current use of composite resin restorations in Canadian dental practices or programs?
7. What factors influence the use of amalgam or composite resin restorations in Canadian dental practices or programs?

Environmental Assessment

8. What are the environmental effects associated with the use of dental amalgams versus composite resin restorations?

Ethics

9. What are the ethical issues associated with the use of dental amalgams compared with the use of composite resin restorations?

Protocol

A detailed protocol was prepared a priori, reviewed by stakeholders external to CADTH, and registered with the PROSPERO database (CRD42017065861). The final version is publicly available.[29]

Clinical Review

Methods

Review Design

To address the first question concerning efficacy, a 2014 Cochrane systematic review (SR)[6] was updated because of the consistency of its objectives, scope, and methods with those planned for the current review. The need of Canadian decision-makers for an updated review of the evidence, combined with the outdated search from the 2014 Cochrane SR, were important factors informing the decision to pursue an update. Recent recommendations informing authors of SR updates indicate that the decision to update should be based on need and priority; and that the update to an existing SR must consider the original SR's quality, as well as the value of modifying its methods.[30]

The 2014 Cochrane SR evaluated both the efficacy and safety of amalgam versus composite resin; although, only the evaluation of efficacy was deemed consistent with the objectives of the current HTA. Specifically, it was decided that a limitation to RCTs may not adequately capture safety or adverse event outcomes of interest and relevance. In addition, the Cochrane SR's analysis of teeth, as opposed to patients, was not deemed to be an ideal approach to the assessment of safety.

Collaboration was initiated with the authors of the 2014 Cochrane SR report and the Cochrane Oral Health Group, involving regular communication with the latter concerning the approach and findings of the update. In particular, discussion was had and consensus reached concerning decisions made during the implementation of the protocol — including study eligibility, plans for analysis and, later, incorporating both efficacy and safety data into a formal update of the Cochrane SR using the data generated from the clinical reviews of this HTA. Essentially, the update sought to build upon the findings concerning efficacy of the 2014 Cochrane SR by identifying and incorporating eligible studies published since the search strategy for that study was run. In general, the objectives informing the original 2014 SR's investigation of restoration failure and survival were adhered to, with methodological modifications made to the definition of the population and outcome of interest (owing to unit of analysis issues reported in the original SR[6]), the search strategy, the procedures for title

and abstract screening and data abstraction, and assessing the quality of the body of evidence identified. A detailed description of these changes is presented in Appendix 3.

The second question considered safety outcomes. Because of the limited analysis of safety in the 2014 Cochrane SR which focused its primary analyses on restoration failure,[6] a *de novo* SR of the evidence describing the comparative safety of dental restorations made of composite resin versus amalgam was conducted.

Standardized Reporting

The report of findings was prepared in consideration of relevant reporting guidelines for SRs; i.e., Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[31] and its extension, PRISMA-Harms.[1]

Literature Search Strategy

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print; In-Process records and daily updates, via Ovid; Embase (1974-) via Ovid; the Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The Cochrane Oral Health Group's Trials Register and Latin American & Caribbean Health Sciences Literature (LILACS) via BIREME databases were searched only for question 1.

The clinical search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. For question 1, the Cochrane SR[6] search was updated. The main search concepts were dental restoration, dental amalgams, and composite resins. For question 1, no methodological search filters were applied. The search was limited to documents published since January 2012 to ensure studies published since the search for the 2014 Cochrane SR[6] were captured, and no language limits were applied. Conference abstracts were included in the search results.

For question 2, the main search concepts were dental amalgams and composite resins. For question 2, a filter was applied to limit retrieval to safety studies. Conference abstracts were excluded from the search results. For the safety search for dental amalgams, the retrieval was not limited to publication year or language. For the safety search for composite resins, the retrieval was limited to documents published since January 2006 but no language limits were applied. See Appendix 2 for the detailed search strategy.

The searches for questions 1 and 2 were completed on June 26, 2017. Monthly alerts were established to update the searches until February 1, 2018. Studies identified in the alerts and meeting the selection criteria of the reviews were incorporated into the analysis if identified prior to the completion of the stakeholder feedback period for the final report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of health technology assessment (HTA) agencies, clinical guideline repositories, SR repositories, economics-related resources, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These

searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Study Eligibility

Eligibility criteria for clinical studies are outlined in Table 1.

Table 1: Study Selection Criteria

	Question 1	Question 2

Population	• Permanent, posterior teeth affected by dental caries (patients of any age)	• Dental caries patients of any age who have been exposed to dental restorations made of composite resin and/or amalgam
		• Where data are available, subgroups were based on the following:
		  ○ patient age (if not otherwise defined within the study):
		  ▪ children (0 to 5 years; 6 to11 years; 12 to17 years)
		  ▪ adults (18 to 64 years)
		  ▪ older adults (65 years and older)
		  ○ genetic susceptibility
		  ○ socioeconomic status
		  ○ remote, rural, and urban settings
		  ○ people with developmental or special needs

Intervention	• Direct, composite resin dental filling restorations, including (where reported) consideration of application techniques:
	  ○ type of composite resin materials
	  ▪ flowable
	  ▪ conventional
	  ▪ compactable
	  ▪ any others not listed
	  ○ bonding materials
	  ▪ universal adhesives
	  ▪ etch-and-rinse
	  ▪ self-etch adhesives
	  ▪ any others not listed
	  ○ filling techniques
	  ▪ incremental
	  ▪ bulk filling
	  ▪ any others not listed
	  ○ application of pins
	  ○ surface areas restored
		• Composite resin as a restorative material for dental caries, including (where reported) consideration of surface areas; i.e., number of:
		  ○ restored surface areas
		  ○ surface years

Comparator	• Direct dental amalgam filling restorations, including consideration of application techniques:
	  ○ bonded and unbonded
	  ○ application of pins
	  ○ surface areas restored
		• Amalgam as a restorative material for dental caries including (where reported) consideration of surface areas; i.e., number of:
		  ○ restored surface areas
		  ○ surface years

Outcome	Clinical efficacy, as defined by the following outcomes:
	• primary:
	  ○ restoration failure rate[a]
	• secondary (i.e., reasons for failure):
	  ○ secondary caries, restoration fracture
	• tooth fracture
		All adverse events, including:
		• toxicity
		• sensitivity
		• allergic reaction
		• injury

Table 1: Study Selection Criteria

Time Frame	• January 2012 to present (in accordance with an update to Rasines Alcaraz et al.[6])	• January 2007 to present
Study Design	• RCTs ○ minimum 3-year follow-up	• RCTs; primary, non-randomized studies that directly compare composite resin and amalgam restorative materials

RCTs = randomized controlled trials.

[a] For question 1, in accordance with the original Cochrane SR, restoration failure incorporated data describing restoration survival.[6]

Full-text publications that met the criteria outlined in Table 1 were included.

For question 2, no limits on the age of patients, types of composite resin, or amalgam dental restorations were imposed. Where reported for both treatment groups, exposure was defined by surface area (either the number of surface areas per type of material per person) or the surface years (the number of surfaces per type of material per person weighted by the number of years present) per type of material per person — in accordance with input provided by clinical experts. All adverse events were considered, including toxicity (e.g., Hg levels; BPA levels and associated neurologic function, renal function, immune function, and reproductive function; fetal and neonatal effects; neurobehavioural and psychosocial function; physical development), sensitivity (e.g., oral lesions, post-operative sensitivity, phototoxic reactions), allergic reactions (e.g., oral dermatitis, stomatitis, photoallergic reactions), and injury (e.g., sustained during placement of the restoration).

Exclusion criteria

For question 1, exclusion criteria established in the 2014 Cochrane SR that was updated for this HTA[6] were used. Specifically, studies were excluded if they focused on restorations in anterior teeth (where amalgam is rarely used), deciduous teeth (generally known as “baby” teeth), and/or reported only on endodontic restorations. Further, because short-term follow-up in the study of dental restorations is less informative,[32] studies with less than three years of follow-up were excluded. Study designs of interest were limited to randomized controlled trials (RCTs), only.[6] Further, reports published prior to 2012 were excluded.

For question 2, while no restrictions were imposed on the study follow-up duration, studies that did not report primary research data directly comparing composite resin and amalgam restorations were excluded in order to maximize the scientific rigour of included studies for the review. Consequently, reviews, meta-analyses, and HTAs were also excluded, as were in vitro and modelling studies. Further, reports published prior to 2007 were excluded in accordance with clinical expert feedback indicating that composite resin materials have changed over time and comparisons with earlier materials were likely to be less relevant to the present day.

For both questions 1 and 2, eligible sources were full, published, or unpublished reports; i.e., there were no conference or meeting abstracts or other summaries that lacked detail describing study methods and findings included in the source material. Duplicate publications were excluded, as were multiple publications of the same study, unless they provided unique methodological details and/or findings of interest.

Study Selection

Two reviewers (SDK, KS) independently screened titles and abstracts of all citations using standardized criteria operationalized using Distiller SR.[33] Title and abstracts deemed potentially relevant by either reviewer were retrieved in full. The same reviewers then independently applied the criteria outlined in Table 1 to each full-text report and compared their selections, resolving all discrepancies through discussion and consensus, and involving a third reviewer (SMM), as necessary. Ongoing discussion among reviewers occurred during both phases of screening to review discrepancies and establish consensus on the application of selection criteria.

The protocol[29] was intended to calculate Kappa statistics for both the title and abstract and full-text phases of screening. The protocol was amended, limiting calculation of Kappa statistics to the full-text phase of screening, only. This was because of the inclusive procedure for title and abstract screening that rendered any citation deemed eligible by either reviewer to be included for full-text scrutiny; thereby precluding the calculation of agreement for these citations. Accordingly, overall weighted Kappa statistics measured agreement between reviewers for each review addressing questions 1 and 2, respectively. Calculated values were interpreted as follows: less than 0.20 as slight agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as substantial agreement, and greater than 0.80 as almost perfect agreement.[34]

Data abstraction

Data from included reports were collected, including:

- first author's name, publication year, country, and funding sources
- study design, analytical approach, and any subgroup analyses of interest
- for question 1:
  - number and types of restorations
  - a description of the intervention, comparator, and, where reported, the application technique(s) used to place the restoration
  - restoration failure rate and reasons for failure (i.e., secondary caries, tooth fracture)
- for question 2:
  - number, age, sex, remote/rural/urban settings, socioeconomic status, and restoration types of study participants (where reported)
  - a description of the intervention, comparator, and, where reported, the numbers of surface areas and/or surface years
- description of outcomes reported, follow-up duration, and study loss to follow-up
- findings and conclusions regarding the outcomes and subgroups of interest.

Data from each included study were abstracted into Microsoft Word tables by one reviewer and verified by a second reviewer, with disagreements resolved through discussion and consensus. Standardized forms were used to inform the data abstraction process.

In accordance with PRISMA-Harms,[1] additional information for question 2 was later abstracted from each of the reports included in this review. Specifically, data describing whether study outcomes were measured actively or passively were collected and reported as part of the study characteristics described in Appendix 8. Causal associations, as described by the study authors, were considered as part of the discussion.

Risk of Bias of Included Studies

For both questions 1 and 2, the Cochrane Risk of Bias Tool[35] was used to assess the included RCTs. The Cochrane Risk of Bias Tool[35] solicits judgments for seven items across six domains, considering selection (i.e., random sequence generation and allocation concealment), performance (i.e., blinding of participants and personnel), detection (i.e., blinding of outcome assessors), attrition (i.e., incomplete outcomes data), reporting (i.e., selective reporting), and "other" biases (i.e., as identified). For each item, a judgment of "Low Risk of Bias," "High Risk of Bias," or "Unclear Risk of Bias" was assigned.

Two researchers piloted forms and independently assessed risk of bias for each eligible report identified. Where included reports from a trial were additional to the first, or primary, publication(s), and cited former publications rather than describing the study methods in detail, references to protocols or design and methods papers were used to retrieve these publications and incorporate relevant information into the assessments. Disagreements between reviewers were resolved through discussion and consensus, and involving a third reviewer (SMM), as necessary. Whereas the findings from these assessments were not used to further exclude studies from the review and analyses, they are described alongside the study findings in order to provide context.

Quality Assessment of the Body of Evidence

Whereas the 2014 Cochrane SR conducted a quality assessment of the body of evidence by outcome using Grading of Recommendations Assessment, Development and Evaluation (GRADE), neither the review of efficacy nor that of safety for this HTA included assessments using GRADE.

Data Analysis and Reporting

Narrative syntheses were undertaken to describe the direction and size of observed effects across outcomes and studies. This employed the use of detailed data tables describing study characteristics and results (Appendices 8 and 9, respectively), supplemented by a summary description of the findings of each included study and report by outcome. Following an assessment of clinical and methodological heterogeneity between studies, statistical pooling (meta-analysis) was deemed to be unfeasible.

Results

Quantity of Research Available

Research Question 1: Efficacy

The electronic literature search identified a total of 517 citations, from which 21 were identified as potentially relevant and retrieved for full-text scrutiny. One report was retrieved from the grey literature. Of these 22 potentially eligible reports, one was found to eligible and included.[36] The report selection process is outlined in Appendix 4 using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

The weighted overall Kappa statistic indicated that initial agreement at the full-text phase of screening was perfect at 1.0.

Research Question 2: Safety

The electronic literature search identified a total of 5,860 citations, of which 68 were identified as potentially relevant and retrieved for full-text assessment. One report was retrieved from the grey literature. Of these 69 potentially eligible reports, 10 were found to eligible and included.[36-45] The report selection process is outlined in Appendix 4 using a PRISMA diagram.

The weighted overall Kappa statistic indicated initial agreement at the full-text phase of screening generated a value of 0.49 (95% confidence interval [CI] 0.39 to 0.79), indicating moderate agreement.

Lists of included and excluded citations for both research questions — with details describing the rationale for those excluded — are presented in Appendix 5 and Appendix 6, respectively.

Characteristics of Included Studies

Of the 10 unique reports that were found, one was eligible for research questions 1 and 2,[36] while the remaining nine were only eligible for research question 2.[37-45] These 10 reports described the results from three unique RCTs, for which characteristics are detailed in Appendix 8.

The first RCT was conducted by Kemaloglu et al.[36] This trial generated one report that was eligible for both research questions. In this trial, 50 teeth were randomly assigned to either amalgam or composite resin restorations in 25 adult patients between the ages of 18 and 60 years. Each patient had at least two carious lesions at baseline, allowing for a split-mouth design that featured each patient having at least one tooth randomized to amalgam and one tooth randomized to composite resin. Authors report the use of dispersed-alloy amalgam placed with a bonding agent (i.e., Amalgambond), and Quixfil composite resin placed with an etch-and-rinse adhesive system (XP Bond). The techniques used for restoration placement were described in detail and standardized across two dental surgeons. The study was conducted at one clinic site in Turkey. The trial duration of follow-up was three years, and outcomes were measured at “baseline” (i.e., two weeks post-intervention) and then at three, six, 12, and 36 months. Funding/support was reported as “Nil”.[36]

The second RCT was the New England Children’s Amalgam Trial (NECAT). Of note, the NECAT was one of two studies contributing to the effifacy analyses in the 2014 Cochrane SR.[6] The NECAT also generated additional reports describing other outcomes — including five that were exclusively eligible for research question 2.[37,38,40,42,45] A total of 534 children between the ages of six and 10 years with at least two carious lesions in either deciduous or permanent teeth at baseline were randomized to either type of dental restoration for the duration of the trial. The techniques used for restoration placement were reported as standard procedures, which were standardized across sites and practitioners.[46] The study was conducted across two sites in the Northeastern US. The trial duration of follow-up was five years, and it was funded by the National Institute of Dental and Craniofacial Research (U01 DE11886).

The third RCT was the Casa Pia Children's Amalgam trial. The Casa Pia trial was likewise one of the two studies informing the primary efficacy analysis in the 2014 Cochrane SR updated as question 1 of the clinical review.[6] Similarly, the Casa Pia trial generated multiple publications reporting different outcomes — four of which were exclusively eligible for research question 2.[39,41,43,44] This RCT randomized 507 children between the ages of eight

and 12 years with at least one carious lesion at baseline to either amalgam or to composite resin restoration(s). The placement of restorations was standardized across dental care providers in the study, and individual treatments were described as being "…essentially randomly assigned…"[47] across study dentists to account for the possibility of provider effects. The trial was conducted in Portugal within the Casa Pia school system, which is comprised of seven school sites. Investigators followed both groups for seven years and received funding from the National Institute of Dental and Craniofacial Research (grant U01 DE11894).

Outcomes and Measures in Included Reports

Details describing the outcomes and measures within the included reports in the clinical reviews can be found in Appendix 8: Study and Report Characteristics — Clinical Review. A summary of these is subsequently described by research question.

Research Question 1: Clinical Efficacy

The one included report[36] addressing efficacy described restoration failure. Study investigators reported the use of modified United States Public Health Service (USPHS) criteria (Ryge).[36] These six criteria included: retention; marginal adaptation; anatomical form; marginal discoloration; surface texture; and secondary caries. For each criterion, a judgment of "Alpha" (i.e., best), "Bravo" or "Charlie" (i.e., worst) was rendered at each of the four follow-up time points – with the exception of retention and secondary caries, for which "Bravo" was not an applicable category. Restoration failure was calculated using a formula that reportedly considered "…the number of unacceptable restorations…"[36]. Methods for ascertaining and distinguishing 'acceptable' from 'unacceptable' restorations were not reported.

Research Question 2: Safety

The safety outcomes reported in the 10 eligible reports[36-45] are shown in Table 2.

Table 2: Harms Outcomes in Eligible Reports

Study	Report	Type of Harm	Harms Outcome of Interest
NECAT	Bellinger et al. (2007)[45]	Toxicity	Neuropsychological function
			Urinary mercury
	Bellinger et al. (2008)[38]		Psychosocial status
	Shenker et al. (2008)[40]		Immune function
	Barreregard et al. (2008)[42]		Renal effects
	Maserejian et al. (2012)[37]		Physical development
Casa Pia	Lauterbach et al. (2008)[43]		Neurological symptoms
	Woods et al. (2007)[44]		Urinary mercury
	Woods et al. (2008)[41]		Renal effects
	Woods et al. (2009)[39]		Urinary porphyrin excretion
Kemaloglu et al. (2016)[36]		Sensitivity	Post-operative sensitivity

Injury

No eligible studies were identified addressing outcomes describing injury.

Allergic reaction

No eligible studies were identified addressing outcomes describing allergic reaction.

Toxicity

Outcomes relevant to toxicity were reported across nine papers[37-45] and included neuropsychological, psychosocial, neurological, immune and renal function, physical development, urinary mercury and porphyrins harms.

Neuropsychological function was described in one report from the NECAT study using, as its primary outcomes measure, administration of the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) at baseline, and at years three and five.[45] A secondary measure included the Wechsler Individual Achievement Test (WIAT), also administered at baseline, and at years three and five. Additional secondary measures included a number of domain-focused tests (detailed in Appendix 8) administered at one, two, and four years.

Psychosocial function was reported in one paper from the NECAT study, using as its primary measure the change in adjusted mean scores between baseline and five years on the parent-reported Child Behavior Checklist.[38] The reported Child Behavior Checklist was used to assess changes in mean scores across four composite scales, including competence, internalizing and externalizing behaviour problems, and total problem behaviours — each of which is informed by a series of 12 subscales. Study authors also reported the use of the child-reported Behavior Assessment System for Children (BASC - SR) at five years follow-up.[38]

Neurological outcomes were reported in one paper from the Casa Pia study, which annually evaluated neurological hard signs, as well as the presence of neurological soft signs (and their severity, when present) and positional tremor.[43] Specifically, neurological hard signs were defined as indicators of "…damage to specific neural structures and, in clinical practice, are used to localize the site of lesion or dysfunction..."[43] and neurological soft signs were defined as "… subtle signs of central nervous system dysfunction that have no localizing value…".[43]

Immune function was evaluated in one report from the NECAT trial, measured using white blood cell count, B cell, T cell, monocyte, and neutrophil function measured at baseline; five to seven days; and at six, 12, and 60 months.[40]

Renal effects were measured in both the NECAT and Casa Pia studies and reported within two included papers — one from each trial.[41,42] While the NECAT authors reported the measurement of markers of glomerular and tubular kidney function — including urinary excretion of albumin; alpha 1-microglobulin; gamma glutamyl transpeptidase; and N-acetyl-beta-D-glucosaminidase at years one (gamma glutamyl transpeptidase, only), three, and five [42] — Casa Pia investigators measured glutathione S-transferases alpha, glutathione S-transferases pi, and albumin, and tested for the presence of microalbuminuria in yearly age cohorts.[41] These analyses further considered the importance of sex in examining measures of renal function.

Physical development was reported in one study from the NECAT trial using five-year changes in body mass index, height, body fat percentage, and initiation of menarche, as well as age at first menarche, where observed.[37] All measurements and analyses considered sex as a relevant subgroup.

One report from the Casa Pia trial measured urinary Hg levels as its primary outcome, accounting for race, sex, and number of amalgam surface areas.[44] Another report from the Casa Pia trial described annual measurement of creatinine-adjusted, geometric mean urinary porphyrin concentrations — including uro-, hepta-, hexa-, penta-, precopro-, and coproporphyrins[39] — including a subgroup analysis by age conducted in eight- and nine-year-olds.

Some papers primarily reporting toxicity outcomes also reported the number of amalgam surface areas[40,43-45] and/or urinary Hg levels[39-42,44,45] per treatment group as exposure variables. And in some of these reports, these variables were used to run additional, secondary, dose-response analyses.[40,42,45] Where data describing these variables were reported quantitatively to describe follow-up findings concerning the originally randomized treatment groups, they are accordingly detailed in Appendix 8 and Appendix 9.

Sensitivity

Sensitivity was reported in one trial,[36] measured as post-operative pain at baseline (two weeks post-intervention), at six, at 12, and at 36 months using thermal stimuli (i.e., cold) and a patient-reported visual analogue scale (VAS) using a line marked from zero to 10 centimetres.

Risk of bias of included studies

A tabulated summary of the risk of bias assessments using the Cochrane Risk of Bias Tool[35] appears in Appendix 7. Overall, each of the included studies exhibited some risk of bias. In particular, risk of performance bias was high in all of the included studies, owing to the visually discernible difference between composite resin and amalgam restorations; consequently, it was impossible to blind participants and personnel to the use of these interventions. Notably, this confers the potential for some residual risk (however unlikely) that patient or provider knowledge of the intervention they were exposed to could impact behaviour that may then affect the harms outcomes, especially those that were subjectively measured. An overall trend was that reports of the NECAT[37,38,40,42,45] generally demonstrated a lower risk of bias compared with those from the Casa Pia[39,41,43,44] or Kemaloglu et al.[36] trials. A summary of the risk of bias assessments is subsequently reported by research question.

Research Question 1: Efficacy

The risk of selection bias in the report by Kemaloglu et al.[36] was variable across items within this domain; i.e., investigators appropriately generated the random sequence (low risk of bias) but did not clearly report their approach to allocation concealment (unclear risk). With respect to the efficacy outcome of restoration failure, the risk of detection bias was high, as outcome assessors could not be blinded. The risk of attrition bias was unclear, as a judgment could not be rendered concerning the reporting of incomplete outcomes data (i.e., five of 25 patients were reported as having been lost to follow-up; no reasons for this were reported and it was unclear whether this could be related to restoration failure).[36] Similarly, the trial was judged to have an “unclear” risk of reporting bias because it could not be ascertained whether the outcomes were pre-specified. Lastly, the trial demonstrated a “high” risk of other potential sources of bias owing to discordance between the stated outcome and measures of interest, and the analyses and conclusions reported.

Research Question 2: Safety

Concerning the NECAT trial and four of its five reports included in this review[37,38,42,45] (supplemented by relevant methods references[38,45,46,48,49] to inform critical appraisal of the study methods), the risk of selection bias was deemed to be "low." One report from a sub-study of immune function, however, described soliciting consent from 257 of 534 study participants, and recruiting only 66 (citing the fear of blood draws as the primary reason for refusal).[40] This lack of clarity was deemed to constitute an "unclear" risk of selection bias — primarily as the approach to selecting the 257 invited participants was not described and the implications for random sequence generation and allocation concealment were similarly unclear. Likewise, the blinding of outcome assessors was reported in all of the NECAT papers,[37,38,40,42,45] earning a judgment of "low" risk of bias for this item and, by extension, for the domain assessing detection bias. As for attrition bias, three of the five of the NECAT papers[37,38,45] earned a "low" risk of bias in this domain. In the remaining two,[40,42] one reported the findings of their primary, comparative analyses of amalgam and its effects on renal outcomes with large numbers of missing patient data and an insufficient explanation as to the reason for this,[42] earning this report a "high" risk of bias. And the risk of attrition bias was deemed to be "unclear" in another NECAT report investigating the immunotoxic effects of amalgam,[40] where reasons for missing data — and their potential impact on bias — were not clearly reported. Reporting bias was judged to be "low" in four of the five NECAT reports.[37,38,42,45] The remaining NECAT report[40] was deemed to warrant a "high" risk of reporting bias owing to apparent discordance between pre-specified outcomes and those described in the reports of findings. Finally, there were no additional sources of bias identified in four of the five included NECAT reports,[37,38,40,42] whereas one report described intention-to-treat analyses but failed to provide details as to their procedure for handling missing data.[45] This resulted in an "unclear" risk of bias judgment for this report.

The Casa Pia trial — as reported in the four papers included in this review[39,41,43,44] and the referenced methods publications consulted[47,50,51] — neither reported their methods for random sequence generation nor allocation concealment transparently, earning this trial a judgment of "unclear" for risk of selection bias. The blinding of outcome assessors was neither reported clearly in any of the reports,[39,41,43,44] nor their referenced methods publications, necessitating a judgment of "unclear" for risk of detection bias. Incomplete and missing data were identified across all four of the included reports.[39,41,43,44] In two of these, the numbers analyzed were not reported, rendering a judgment of "unclear" risk of attrition bias.[41,44] The other two reports both indicated large numbers of missing data, ranging from 149 missing at the end of follow-up from 479 analyzed at baseline in the report of porphyrin excretion[39] to 278 missing at the end of follow-up from 506 analyzed at baseline from the report of neurological outcomes.[43] Reasons for missing data were not described in the former report[39] and were described as being related to the availability of study participants during outcome measurement time points in the latter paper.[43] Whereas missing data were reasonably balanced between groups in both papers, the lack of an explanation for the missing data in the paper describing porphyrin excretion earned this report an "uncertain" risk of attrition bias.[39] For the other report,[43] the magnitude of data missing and its unclear effect on the outcomes reported — particularly considering the reported rationale for its being missing — earned this report a "high" risk of attrition bias. Reporting bias was judged to be "low" in two of the four Casa Pia papers.[41,44] In two of the remaining included reports,[39,43] a "high" risk of reporting bias was ascertained, owing to apparent discordance between pre-specified outcomes and those described in the reports of findings. Finally, no additional sources of bias were identified in three of the four included reports from the Casa

Pia trial.[39,41,43] The remaining report [44] was deemed to have an "unclear" risk of bias, as some of the reported analyses were not pre-specified.

As the risk of selection bias in the trial by Kemaloglu et al.[36] was independent of the outcome, the resulting assessment of low risk of bias for randomization and unclear risk of bias for allocation concealment is the same as described earlier. The risks of other biases were, however, unique to the safety outcome of post-operative sensitivity. In particular, the risk of detection bias for the safety outcome was unclear in this trial; investigators described the assessment of post-operative sensitivity as blind.[36] Nevertheless, the procedure for operationalizing a blinded assessment of post-operative sensitivity was neither clearly reported, nor intuitively ascertainable. As with the risk of attrition bias concerning efficacy (abovementioned), the risk of attrition bias was likewise unclear as it concerned post-operative sensitivity (i.e., five of 25 patients were reported as lost to follow-up); however, reasons for this were not reported and it was unclear whether this could be related to post-operative sensitivity.[36] Similarly, the trial earned an "unclear" risk of reporting bias because it was not apparent whether the outcomes were pre-specified, as no protocol was available. Finally, this trial was deemed to be at a "high" risk of other potential sources of bias owing to its lack of clarity in reporting the post-operative sensitivity; i.e., rather than report scores, or differences in mean scores, variations in scores across time were reported as "ranks".[36]

Summary of Study Findings

Research Question 1: Clinical Efficacy

Detailed findings from the 2014 Cochrane SR can be found in the report by Rasines Alcaraz et al.[6] Our report describing the update to this SR includes a brief summary of its findings (which follows), but focuses on describing the evidence identified since its 2013 search.

The 2014 Cochrane SR identified seven eligible trials, of which two employed parallel-group designs and five used split-mouth designs. The SR authors judged all seven trials to be at high risk of bias, emphasizing important limitations with the five split-mouth studies. Consequently, their primary analyses were based on the two parallel studies: the NECAT and Casa Pia trials. These two RCTs contributed a total of 3,265 composite restorations (753 from the NECAT and 892 from the Casa Pia trial) and 1,935 amalgam restorations (509 from the NECAT and 856 from the Casa Pia trial) from permanent, posterior teeth across five- and seven-year durations of follow-up, respectively.[6] An assessment of illustrative comparative risks resulted in an assumed risk for amalgam of 75 per 1,000 (95% CI not reported [NR]) for restoration failure; 57 per 1,000 (95% CI NR) for secondary caries; and 14 per 1,000 (95% CI NR) for restoration fracture (Appendix 9). For composite resin, the illustrative comparative risk assessment indicated a corresponding risk of 142 per 1,000 (95% CI 114 to 176) for restoration failure; 122 per 1,000 (95% CI 95 to 156) for secondary caries; and 12 per 1,000 (95% CI 6 to 23) for restoration fracture.[6] Based on a GRADE rating of low-quality evidence, their results demonstrated that, when compared with amalgam, composite resin restorations were associated with statistically significantly higher failure rates (risk ratio [RR] 1.89; 95% CI 1.52 to 2.35, $P< 0.001$) and risk of secondary caries (RR 2.14; 95% CI, 1.67 to 2.74, $P< 0.001$). There was no statistically significant difference between treatments in the risk of restoration fracture (RR 0.87; 95% CI 0.46 to 1.64, $P = 0.66$). Whereas, according to the Cochrane handbook,[35] assessments of heterogeneity for the primary analyses of restoration failure and secondary caries indicated that heterogeneity was considerable (I^2 = 87% and 92%, respectively), the authors explained that, because the direction of these effects was consistent across both RCTs for these outcomes, meta-analyses were deemed appropriate and thus undertaken.[6] In

subgroup analyses of the five split-mouth studies, the direction of treatment effects for failure rate was consistent with that of the primary analysis (RR 1.33; 95% CI 0.84 to 2.11, *P* = 0.23), whereas there was no difference in secondary caries risk found between composite resin and amalgam restorations (RR 1.3; 95% CI 0.34 to 4.97, *P* = 0.7).[6]

In updating the Cochrane SR, one eligible RCT was identified, the results of which are presented in detail in Appendix 9. Although the trial authors reportedly measured restoration failure, the manner in which they presented the data precluded statistical pooling with those in the Cochrane SR; specifically, it was unclear how the data from the clinical evaluations were used to inform the reported findings. Nevertheless, based on an analysis of 40 posterior teeth from 20 adult patients (five patients were lost to follow-up), the authors concluded that the "overall failure rate … was 0%" after up to three years of follow-up.[36] Similarly, the proportion of "Alpha" ratings (i.e., no caries) was 100% for both amalgam and composite resin restorations at all follow-up time points in the study, suggesting that zero events of secondary caries occurred in both arms of the trial.

Research Question 2: Safety

Toxicity

Neuropsychological evaluations were carried out on a variable number of children in the NECAT (between 328 and 436 of the 534 children randomized), depending on the outcome measure/subscale. The evaluations found no statistically significant difference between treatment groups on any overall measure of neuropsychological function.[45] However, analyses indicated a statistically significant between-group difference on two subscales. One of four WRAML, or Wide Range Assessment of Memory and Learning, subscales — the Number-Letter Memory Scale — favoured amalgam with a mean change in score from baseline to year 4 of follow-up for the amalgam group of 0.3 (standard error [SE] ± 0.10) and –0.3 (SE ± 0.1) for the composite resin group (*P* = 0.002). On the other hand, one of four subsections of the Trail Making Test — "Part B: time to complete" — favoured the composite resin group with a mean change in score from baseline to year 4 of follow-up in the amalgam group of –45.6 (SE ± 1.0), and of –50.4 (SE ± 1.1) in the composite resin group (*P* = 0.002). Data for each of the outcome measures applied are reported in detail in Appendix 9.

Authors of this report from the NECAT also described urinary Hg levels and amalgam surface areas at five years of follow-up for each treatment group, primarily using these values as predictors to run additional, secondary analyses describing neuropsychological findings as a function of these exposures.[45] Both predictors were reported by randomized treatment group; however, and the urinary Hg levels were deemed particularly relevant in terms of assessing comparative safety, a significantly higher level of mean urinary Hg was found in children randomized to amalgam at five years of follow-up — i.e., 0.9 mcg/g creatinine (range, 0.1 to 5.7 mcg/g creatinine) — as compared with children in the composite group — i.e., 0.6 mcg/g creatinine (range, 0.1 to 2.9 mcg/g creatinine) [*P* < 0.001; 95% CIs NR].[45] In another report from the Casa Pia trial, urinary Hg levels were reported as a primary outcome of interest.[44] Children in both treatment groups had comparable urinary Hg levels at baseline; i.e., 1.5 mcg/L (standard deviation [SD] ± 1.2; range 0.1 to 7.7) for amalgam and 1.4 mcg/L (SD ± 1.1; range 0.0 to 8.6) for composite resin. Urinary Hg levels became significantly higher in children assigned to amalgam through years 2 to 6, with a peak level of 3.2 mcg/L in year 2 post-intervention [*P* < 0.001; 95% CIs NR]; levels for the composite resin group were only reported graphically and not quantitatively.[44] Notably, however, in follow-up year 7, urinary mercury in the amalgam

group had dropped to a level comparable to that of baseline (reported narratively and graphically, only). Importantly, the difference between treatment groups was no longer statistically significant, indicating a reduction in urinary mercury excretion in those receiving dental amalgam restorations across time.[44] Subgroup analyses of sex differences in urinary mercury excretion also found statistically significantly higher levels in females treated with amalgam as compared to males ($P < 0.05$); whereas no sex difference was observed in the composite resin group. Detailed data describing the findings reported on the originally randomized treatment groups (i.e., using dental material type as the predictor) are presented in Appendix 9.

Psychosocial evaluations were completed on a subset of children in the NECAT study (i.e., 395 for the child behaviour checklist and 426 for the BASC-SR analyses).[38] While no statistically significant group difference was identified by the competence or externalizing behaviour composite scales, a statistically significant group difference was found by both the internalizing behaviour (mean change in score from baseline to five years of follow-up: amalgam group = –3.8 [SD ± 0.6]; composite resin group = −2.1 [SD ± 0.6]; $P = 0.03$) and total problem behaviour (mean change in score from baseline to five years of follow-up: amalgam group = −3.3 [SD ± 0.7]; composite resin group = −2.1 [SD ± 0.7]; $P = 0.007$) composite scales — both differences favouring the amalgam group, with greater deficits observed in the composite resin group. The BASC-SR evaluations produced four global scores derived from a series of subscales and compared five-year follow-up results across treatment groups. Similarly, these analyses indicated no statistically significant difference between groups in two of the four global scores (i.e., school and clinical maladjustment). However, the remaining two global scores indicated a statistically significant between-group difference that both favoured the amalgam group (personal adjustment amalgam group mean score = 53.3 [SD ± 0.6]; composite resin group mean score = 51.3 [SD ± 0.6]; $P = 0.005$) and the emotional symptoms index amalgam group (mean score = 44.6 [SD ± 0.6]; composite group mean score = 46.3 [SD ± 0.6]; $P = 0.05$). Detailed data, including those describing subscale results as reported, are presented in Appendix 9.

Neurologist-administered, annual evaluations of neurological symptoms in the Casa Pia trial — including the presence of neurological hard signs, soft signs, and positional tremor — found no statistically significant difference between the amalgam and composite resin treatment groups at any point in time.[43] Between years 3 and 7, additional measurements were taken to evaluate the severity of neurological soft signs observed; likewise, these assessments showed no statistically significant between-group differences in scores at any point in time. Data are detailed in Appendix 9.

Immune function was measured in a substudy of the NECAT that analyzed data for 59 of 257 children invited to participate (35 from the amalgam group and 31 from the composite resin group). Authors report that the characteristics of children in the substudy were similar to those of the overall study population.[40] Measurement of total white cell counts, T cell, B cell, neutrophil, and monocyte responsiveness indicated no statistically significant differences between treatment groups at any one of five points in time across the five-year study follow-up (Appendix 9).

The physical development of children was also compared across groups in the NECAT study, including 474 of the 534 children originally randomized.[37] The authors report no between-group differences in age-adjusted, mean body mass index-for-age Z scores, body fat percentage, or height throughout the five-year study follow-up. Additional, exploratory analyses of menarche outcomes in females investigated 113 participants and were

restricted to one study site. These analyses indicated that girls in the composite resin group were statistically significantly less likely to have reached menarche during study follow-up compared with those in the amalgam group (48% versus 67%; hazard ratio = 0.57, 95% CI 0.35 to 0.95, *P* = 0.03). Nonetheless, an examination of age at first menarche indicated no statistically significant difference between treatment groups among those who had reached first menarche (amalgam group mean age in years = 12.3 [SD ± 1.0]; composite group mean age in years = 12.5 [SD ± 1.1]). Data are presented in Appendix 9.

Renal function was measured in both the NECAT and Casa Pia trials and described in two reports, one from each study, included in the clinical review.[41,42] In the paper generated from the NECAT study,[42] 490 children were included in the primary analyses where no statistically significant group difference in biomarker levels or prevalence of high biomarker values was reported. However, the authors do report statistically significantly higher odds of microalbuminuria (MA) observed in the amalgam group in a repeat-measures logistic regression analysis at years 3 or 5 (number with MA/number analyzed, year 3: amalgam group = 18/135 [13%], composite resin group = 15/148 [9.5%]; number with MA/number analyzed, year 5: amalgam group = 30/193 [16%]; composite resin group = 18/186 [9.7%]; *P* = 0.03). Notably, the authors suggest this finding may be due to chance or confounding and should be further investigated for corroboration. In particular, they indicate that albuminuria is common in the general population, including in children, and can occur as a result of everyday exposures such as extreme physical exertion or infections causing fever.[42] Notably, in their report of renal function, authors from the Casa Pia trial report on microalbuminuria in yearly age cohorts and found no difference between the treatment groups.[41] Similarly, no statistically significant between-group differences were found in measures of all other renal biomarkers. Detailed data for both studies and their measures are tabulated in Appendix 9.

Another report generated from the Casa Pia trial presented the urinary porphyrin excretion in 479 children (i.e., all those for whom porphyrin data were available).[39] No statistically significant differences were found in any of the primary analyses comparing the randomized treatment groups, nor in a series of subgroup analyses (i.e., by age, race, and sex). The authors emphasized “incipient increases” observed in a subgroup analyses of eight- and nine-year-old participants; however, they indicated that the observed, non-statistically significant effects are far below the threshold at which renal function is expected to be affected. While little quantitative data were reported (i.e., findings regarding porphyrin levels were presented within graphs and significance test results were reported qualitatively), data from the report are presented in Appendix 9.

Sensitivity

The report of post-operative pain from Kemaloglu et al.[36] did not provide data describing raw VAS scores observed between restoration types. However, the report did describe the results of significance tests between restoration types, indicating no between-group differences in post-operative pain at baseline (two weeks post-intervention), or at six or 12 months.[36] Nonetheless, the authors report that VAS scores were found to differ significantly (*P* < 0.05; raw scores were not reported) at the 36-month evaluation, favouring composite resin restorations. The data, as abstracted from the article, are presented in Appendix 9.

Summary of Results

To address the comparative clinical efficacy and safety of dental amalgam and composite resin, two SRs were undertaken:

- an update to a 2014 Cochrane SR
- a *de novo* SR of the comparative evidence describing safety and harms.

Efficacy

A 2014 Cochrane SR's[6] primary meta-analysis included two parallel-group RCTs describing 3,010 permanent posterior teeth in children (at baseline), and found a statistically significantly higher risk of restoration failure and secondary caries in composite resin versus amalgam. A subgroup analysis of five split-mouth RCTs likewise found a significantly higher risk of restoration failure with composite resins compared to amalgam but no difference between groups in secondary caries risk.

The update identified one eligible study — a 2016 split-mouth RCT that analyzed restoration performance in 40 teeth throughout three years of follow-up, with an unclear or high risk of bias in most domains assessed (this study was also eligible for the question addressing safety, which follows).[36] Authors reported zero events of restoration failure and secondary caries in either treatment arm and concluded that "…survival rate was 100% for both of the restoration types and they were found to be successful".[36] Because of methodological and clinical heterogeneity, incorporation of the data from the 2016 split-mouth RCT identified in the update was not possible with data from the 2014 Cochrane SR. The findings from the 2016 split-mouth RCT appear to contrast with those of the 2014 Cochrane SR; although, there are several cautions against overinterpreting the findings of the individual study, most notably the small sample size and relatively short follow-up duration (i.e., the minimum sufficient follow-up was deemed to be three years) in the newer study.

Safety

All 10 reports identified in the *de novo* SR addressing safety were generated from RCTs and described either toxicity or sensitivity outcomes in a combined 1,081 patients ranging from six to 60 years of age. Assessments identified a risk of performance bias in all of the studies, in addition to risks of bias from other domains that varied across papers. Statistically significant differences in urinary mercury excretion between composite resin and amalgam patients were reported in both the NECAT[45] and Casa Pia[44] trials through to five and six years of follow-up, respectively. Notably, unadjusted urinary mercury levels at seven years follow-up in the Casa Pia trial were found to no longer differ significantly between treatment groups,[44] suggesting that mercury exposure from dental amalgam restorations may attenuate across time. Whereas one paper from the Casa Pia trial found no between-group differences in any measures of renal effects,[41] and three of four measures of renal function used in the NECAT similarly indicated no statistically significant differences,[42] the prevalence of micoralbuminuria was found to be statistically significantly higher in the amalgam-treated group in years 3 and 5.[42] Similarly, whereas four of five measures of physical development in the NECAT indicated no between-group differences, a subgroup analysis of menarche initiation in females at one study site showed a statistically significantly greater probability in the amalgam as compared with the composite resin group.[37] Likewise, while 10 of 12 measures of neuropsychological function in the NECAT identified no between-group differences, one subscale from each of the remaining two measures suggested a statistically significant difference — one favouring the amalgam and the other, the composite resin group. [45] Again, in an evaluation of psychosocial outcomes from the NECAT, two of four sub-scores for both the primary and secondary measures indicated no statistically significant group difference, whereas the other two sub-scores for both measures did indicate statistically significant differences — all of which favoured the

amalgam group (i.e., scores were less favourable among those in the composite resin group).[38] And while post-operative sensitivity did not differ between amalgam and composite resin restorations at two weeks, and at six and 12 months of follow-up, a statistically significant difference was reported at 36 months of follow-up, favouring the composite resin group.[36] Of note, the authors did not comment on the clinical significance of this latter finding but did elaborate in their discussion that variability in the bonding materials used may have played a role in the post-operative sensitivity findings. Finally, no statistically significant differences between treatment groups were observed in evaluations of neurological symptoms,[43] immune function,[40] and urinary porphyrin excretion.[39]

Economic Evaluation

This section addresses research question 3:

What are the comparative consequences and costs of using dental restorations made of composite resin or amalgam for permanent posterior teeth in Canada?

Methods

Literature review

A literature review was conducted to identify previously published economic models on dental restoration with amalgams or with composite resin. In total, 11 economic evaluations were identified that addressed the economic value of various dental restoration procedures or caries management programs.

One model estimated the financial impact of introducing an amalgam ban in a 15-year period in the US.[52] All other analyses were cost-effectiveness analyses using a decision tree, a Markov cohort model, or a patient-level simulation.[53-62] Two had a time horizon shorter than 15 years,[59,60] while the majority of the remainder adopted a lifetime perspective. A description of these published models can be found in Appendix 10.

None of the models identified compared amalgam with composite resin for the restoration of permanent posterior teeth over the course of a lifetime horizon within a Canadian setting. Therefore, a *de novo* economic model was constructed to address research question 3. Existing economic models provided insights toward developing the model structure, in determining appropriate model assumptions, and possible sources of data inputs relating to disease prognosis.

Methods overview

The objective of the economic analysis was to evaluate the comparative consequences and costs associated with composite resin and amalgam as restorative materials for permanent posterior teeth within a Canadian societal perspective.

As mentioned in the protocol, the outcomes of interest in the cost-consequence analysis were dependent on the results of the clinical and environmental review.[29] At the time of the protocol development, these were expected to include the average lifespan of dental restorative material, the rates of adverse events, and the level of exposure to toxic material throughout the patients' lifetimes or, if the data were limited, over a period shorter than the lifespan of the dental restoration.

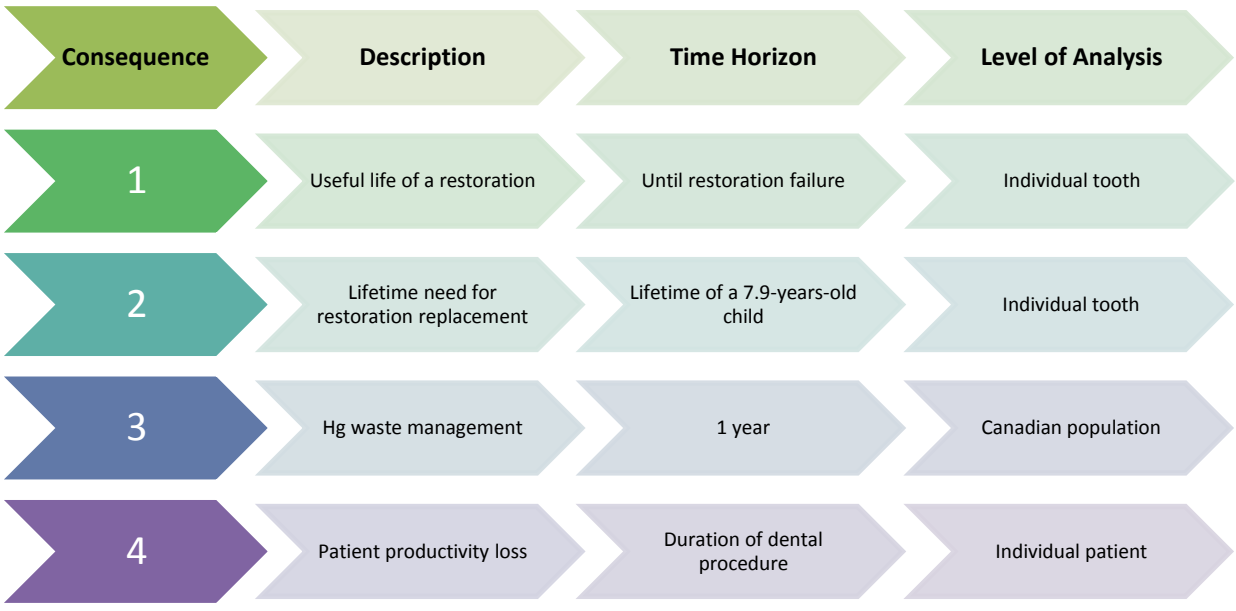
Seven consequences were identified based on the literature review and in consultation with clinical experts involved in the review: useful life of a restoration, lifetime need for restoration replacement, mercury (Hg) waste management, Hg/BPA exposure, adverse events, patient preference, and patient productivity loss. Upon completion of the clinical and economic literature reviews, no information was available to support the consideration of three of the seven consequences. The following three consequences were not explored in the cost-consequence analysis given the following reasons:

- Hg/BPA exposure: no clinical consequences that could be modelled from the clinical review.
- Adverse events: could not be modelled given the findings from the clinical review that reported no discernible effect patterns between treatment groups.
- Patient preferences/utilities: no information on utility measurements in patients with amalgam and/or composite resin restorations of the posterior teeth was identified.

Therefore, the cost-consequence analysis focused on the four consequences listed in Figure 1.

The original level of analysis was expected to be the individual restored tooth; however, during the research phase it was determined that this level of analysis was not appropriate for all consequences. For example, using the country level for Hg waste management may be more meaningful than from a single tooth in view of the small quantities of Hg used for a restoration. Similarly, for productivity loss, the patient-level made more sense as it reflects his/her time spent going to the dentist. The analysis for each consequence is reported under different time horizons. The level of analysis and the time horizon used are listed for each consequence in Figure 1.

Figure 1: Consequences Included in the Analysis



Hg = mercury.

Type of economic evaluation

A cost-consequence analysis was considered the most appropriate approach for this assessment in order to capture the health- and non–health-related consequences associated with different restorative materials for dental caries. Although this approach does not comply to existing Canadian guidelines in the conduct of economic evaluations, it was deemed to be the best approach for this decision problem.[63] Given the policy question, this represents a unique situation whereby the information of interest to decision-makers can vary depending on their role. The cost-consequence analysis permits decision-makers to identify those consequences that are of interest and relevance to them and to perform a trade-off between these consequences. Furthermore, some of the non-health consequences, in particular on the environment, cannot be adequately captured by a cost-utility analysis (i.e., limited literature or guidance on how to link environmental concerns as outcomes in an economic model). By looking at the health- and non–health- related consequences and costs, this economic evaluation captures broader societal consequences and costs (i.e., Hg waste management) that may be important considerations to some decision-makers.

Therefore, a cost-consequence analysis was the chosen approach for this assessment. In a cost-consequence analysis, the consequences (health- and non–health-related) and their respective costs are analyzed and presented separately in a disaggregated fashion. Seven important and clinically meaningful outcomes were of interest to this review, although only four (Figure 1) could be included in the final model because of a lack of data.

Target populations and interventions

The economic analysis focused on Canadians in need of an initial restoration to a posterior tooth. Analyses were performed at the tooth level for consequence numbers 1 and 2. As the clinical data sources used for consequence numbers 1 and 2 included studies exclusively performed in children, the target population was further refined to Canadian children for these two consequences. For consequence number 3 (i.e., waste management), the level of analysis was the Canadian population given the broad environmental impacts associated with different materials for dental restoration. The level of analysis was that of the individual for consequence number 4 (productivity loss).

According to the clinical experts consulted, two- and three-surface restorations are the most commonly performed restorations of posterior permanent teeth (C.Q.: expert opinion, 2017 Dec; S.E.: expert opinion, 2017 Dec). Therefore, all analyses at the tooth and individual-level were conducted to reflect this information.

The two interventions compared in this analysis were amalgam and composite resin used as restorative materials for permanent posterior teeth affected with caries. These two interventions are described in Table 3. Although there are circumstances in clinical practice where amalgam or composite resin may be the favoured restoration material (e.g., amalgam for deeper restorations), this analysis assumed that the tooth assessed would be suitable for restoration by either materials.[64,65]

Perspective

The primary perspective of this analysis was societal. In Canada, 5.5% of the population is covered by a public dental program.[66] The societal perspective includes consideration of the impact of different dental restoration materials to third-party payers, such as private dental

insurances and the dental fees paid out-of-pocket by Canadians who do not have private dental insurance.

Time horizon

The time horizon varied according to the nature of the consequence. For consequence number 1 (useful life of a restoration), the time horizon was defined until restoration failure. For consequence number 2 (lifetime need for restoration replacement), a lifetime horizon was used. In this case a 1.5% discount rate per annum was applied after the first year to costs and consequences in the base-case analysis (0% and 5% discounting in sensitivity analyses).[63] For consequence number 3 (Hg waste management), the time horizon was one year. Finally, for consequence number 4 (productivity loss), the time horizon captured in the cost-consequence analysis reflected the duration of the initial restorative dental procedure. No discounting was therefore necessary for consequences 1, 3, and 4.

Model structure

Table 3 gives an overview of the clinical and cost end points included in each of the four consequences, as well as the respective sources of data used in the analysis. More details on the data sources can be found under the Valuing consequences section of this report and the Cost Estimate sections as well as in Appendix 10. With the exception of consequence no. 2, the value of the consequences was based on calculations described in the Valuing consequences section rather than through more extensive modelling.

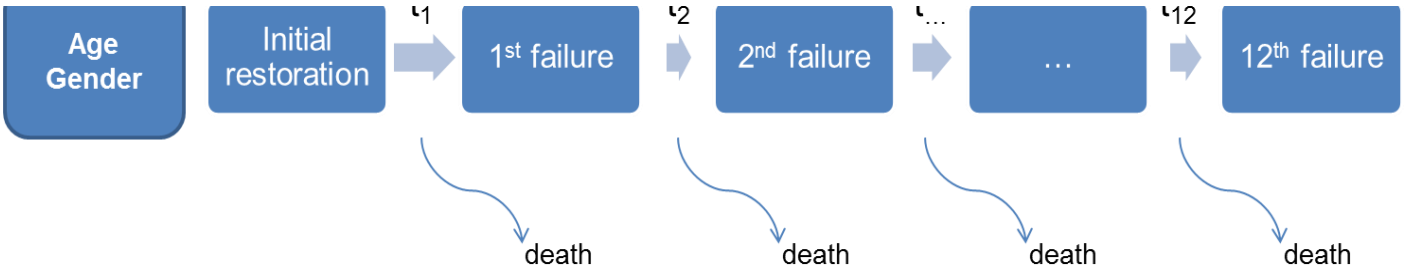
Table 3: Overview of End Points of the Consequences and Costs

No	Consequence	Clinical/ Humanistic or Other End Points	Data Source	Costs	Data Source
1	Useful life of a restoration	• Time to secondary restoration	• Clinical review	• Cost of restoration	• Dental fee schedules
2	Lifetime need for restoration replacement	• Number of replacements needed throughout the lifetime of the tooth	• Clinical review	• Total costs of restorations throughout the lifetime of a tooth	• Dental fee schedules
3	Mercury (Hg) waste management	• Amount of Hg waste per restoration • Amount of Hg waste by restoration removed • Amount of Hg escaping in the waste water	• Environmental review	• Amalgam separator costs (acquisition, maintenance, waste disposal; Hg released in the environment)	• Clinical expert
4	Patient productivity loss	• Time loss due to dental procedure	• Duration of dental procedure	• Cost of time loss	• National statistics on income

A patient-level Markov state-transition simulation was performed to address consequence number 2 (lifetime need for restoration replacement). This was necessary to calculate the expected number of dental restorations throughout the lifetime of a patient's tooth. The model simulated 5,000 individual children with an average age of 7.9, of which 51% were males.[67,68] The model progressed based on time to next restoration, and, once the age of the patient's next restoration was calculated, the model would assess whether the patient

would have remained alive up to that age using Canadian life tables.[69] The structure of the model is shown in Table 6.

Figure 2: Consequence 2 — Structure of the Patient-Level Simulation



t= time to failure (i.e., t_1 = time to first failure).

All calculations were performed using Microsoft Excel 2010. Probabilistic analysis was used for all calculations except for consequence number 3, which was deterministic.

Valuing consequences

Efficacy (consequences numbers 1 and 2)

The clinical review identified one study in addition to those included in the primary analysis of a previously published SR.[6] However, after discussion with the clinical review team and the clinical experts in dentistry consulted as part of this review, the NECAT — one of the two studies included in SR mentioned previously — was judged to be a more appropriate trial to inform the base case of the cost-consequence analysis, based on the following:[36,67]

- The NECAT was conducted in the US (New England area), while the others were conducted either in Turkey or in Portugal for the Casa Pia study.[36,67,70] Thus, the clinical characteristics of the NECAT were felt to be more generalizeable to the patient characteristics in Canada.
- As noted in the Clinical Review, the NECAT generally demonstrated a lower risk of bias compared to the Casa Pia or the Kemaloglu studies.[6,36,67,70]
- The Casa Pia study had implemented a dental caries prevention program at the study's initiation that could have confounded the observed results.[70]
- The Kemaloglu study was small (n = 25 patients) compared to the NECAT (n = 534 patients).[36,67]

Time-to-restoration replacement was the main efficacy parameter for consequences 1 and 2. In the NECAT, replacements were performed for new caries (i.e., carious surface different from the one previously restored on the same tooth), recurrent caries, fracture, restoration loss or other (not otherwise specified) causes.[67] In agreement with the clinical experts, repairs reported in the NECAT were not considered in the economic model as restoration failure since the number of repairs reported was low (i.e., two in the amalgam group and 21 in the composite resin group).[67] The survival curve from the NECAT was digitalized using Digitizelt (Trialware, Germany). A mathematical model was fitted to the curve using the methods and tools developed by Hoyle and Tierney in order to extrapolate the survival curve beyond the five years of the study, as well as to account for parameter uncertainty.[71,72] The average time-to-restoration failure and its SD were calculated from the extrapolated data and used to determine consequence number 1 (useful time of a restoration) and incorporated as a model input to estimate consequence number 2 (lifetime

need for restoration replacement). Although some evidence on the natural history of tooth restoration was found in the medical literature, it was insufficient to allow modelling to a patient's lifetime.[73-77] Therefore, it was assumed that the time-to-failure for each subsequent restoration was independent of any prior restoration to that tooth and it was further assumed that the restoration material for any subsequent replacement would be the same as the previous procedure (see Table 6).

Mercury waste management (consequence number 3)

The sources of Hg waste from an amalgam restoration are multiple and have been described in the literature.[78] A detailed assessment of amalgam, and hence mercury, waste in Canada has been made in the environmental section of this report (see Environmental Impact). Results of the environmental assessment (i.e., Hg waste generated from amalgam placement and removal, Hg waste captured by chairside traps and amalgam separators, Hg waste captured by wastewater treatment plants, and Hg waste reaching surface waters) have been used for this consequence.

Patient productivity loss (consequence number 4)

No study reporting patient or caregiver productivity loss was identified through the literature review. However, as the travel time to the dental office, the waiting time at the dental office, and post-procedure recovery are not expected to be impacted by the choice of dental restoration material, the time required to complete the dental procedure should reflect the incremental difference in productivity loss between restoration materials.

Three studies reporting the time to perform amalgam and/or composite restorations were identified.[60,79,80] One of them reported a summary measure combining amalgam and composite resin restorations and therefore could not be used.[80] Another study performed in 1992 in more than 2,000 two- and three-surface amalgam restorations in the Netherlands estimated the average total treatment time (i.e., tooth preparation, packing, carving, polishing) to be 24.3 minutes (95%CI: 11.3 to 46.5) and 30.0 minutes (95%CI: 15.6 to 59.0) for two-surface and three-surface amalgam restorations, respectively.[79] About 75% of the restorations in that study were performed in posterior teeth.

Tobi et al., using data from a clinical study, reported a median procedure time of 39 minutes for a composite restoration of premolars compared to 22 minutes for an amalgam restoration (i.e., 1.8 times greater).[60] Median procedure time values for molars were 52 and 25 minutes for composite and amalgam restorations, respectively (i.e., 2.1 times greater). These ratios were not felt to be reflective of current practice times by the two experts in dentistry involved in this review. The analysis by Tobi et al.[60] included 41% new restorations and 59% subsequent restorations (partial or complete) of an amalgam restoration. This could have had an impact on the time required for tooth preparation if composite and amalgam groups were not balanced with respect to the proportion of new and subsequent restorations. No information on this was available from the publication. Furthermore, the original clinical study used by Tobi et al. was published in 1991 and both composite resin materials and techniques have evolved since then. In fact, a decrease in composite resin procedure time between 10% and 25% was observed throughout the study period. Based on feedback from clinical experts, it was suggested that the procedure time for a composite resin would take 15% longer (i.e., 25.3 minutes) than an amalgam restoration (C.Q.: expert opinion, 2017 Dec; S.E.: expert opinion, 2017 Dec). This value was used in the analysis of this consequence.

Cost Estimates

Dental procedures (consequence numbers 1 and 2)

The costs of dental procedures were obtained from two different sources:

- public dental programs
- suggested dental procedure fees (for private patients) from provincial dental associations as a proxy of fees paid by private insurances and patients who pay dental services out-of-pocket via an Environmental Scan.

Details of the methodology and results have been published in the report of the Environmental Scan.[81] In the base-case analysis, the fees for two- and three-surface restorations to permanent posterior teeth retrieved from private and public programs were averaged separately for amalgam and composite resin (all tooth types combined) for private and public programs, and then combined into a Canadian weighted average based on a 5.5:94.5 ratio of public:private coverage of the Canadian population (Table 4).[66]

Table 4: Average Procedure Costs for Two- and Three-Surface Restorations (Premolar and Molar Combined)

	Public		Private		Canadian Weighted Average	
	Amalgam	Composite Resin	Amalgam	Composite Resin	Amalgam	Composite Resin
Average	$131.12	$182.90	$172.18	$220.82	$169.92	$218.74
SD	$27.19	$41.11	$37.78	$26.88	$21.33	$27.48

SD= standard deviation.

A similar approach was taken to determine the restoration, crown (excluding laboratory fees, as these are billed as pass-through costs), and extraction costs to inform sensitivity analysis for consequence 2.

Mercury waste management (consequence number 3)

The costs of Hg waste can be subdivided into the cost of amalgam waste management at the dental clinic, the attributable costs at the waste water management plant level, and the costs of managing the consequences of Hg reaching surface water. However, in view of the performance of amalgam separators in removing Hg from dental waste water, the last two elements were felt to generate insignificant costs and thus the analysis for this consequence focused on the costs at the dental clinic. An American publication provided the framework for estimating the costs of amalgam separators and waste disposal.[82] Elements and values were adjusted to reflect a Canadian setting. In particular, the acquisition and installation costs of an amalgam separator were estimated to be $2,000, whereas the annual maintenance costs (i.e., waste collection containers and recycling services) were estimated at $2,200 according to feedback from one of the clinical experts involved in this review (S.E.: expert opinion, 2017 Aug). Considering a useful life of five years for the amalgam separator, costs were annualized to a single dental clinic. They were then multiplied by the estimated number of dental clinics in Canada to determine the annual costs of managing Hg waste in Canada.[83] It was assumed that the costs of dental Hg waste recycling and/or disposal was factored in the price of the amalgam separator maintenance costs (i.e., recycling services) and therefore no other costs related to the disposal and/or recycling of Hg waste were added.

Hourly wages and proportion of the Canadian population employed (consequence number 4)

The national hourly average salary for 15-year-olds and older, from September 2017 obtained from Statistics Canada, was multiplied by the percentage of employed individuals and the time required for dental restorative procedures in order to estimate the productivity loss in consequence number 4.[84,85]

All costs were inflated to 2017 using the consumer price index, as needed.[86]

Sensitivity analysis

All calculations, except those for consequence number 3 (Hg waste management), were performed in a probabilistic fashion (5,000 iterations) to account for parameter uncertainty.

In addition, the scenario and sensitivity analyses described in Table 5 were performed for consequence 1 (useful time of a restoration), consequence 2 (lifetime need for restoration replacement), and consequence 4 (productivity loss).

Table 5: Description of Scenario and Sensitivity Analyses

Scenario/Sensitivity Analysis Description	Consequence			Justification
	1	2	4	
Using the Casa Pia study results (rather than NECAT results) for the time-to-failure	X	X		To address parameter uncertainty
Extreme value analysis of the main efficacy parameter: smallest and largest difference between groups using lower and upper limits of 95%CI from NECAT	X	X		To address parameter uncertainty
All surface average restoration costs	X	X		To address structural (i.e., unknown natural history of an initial restoration in a child) and parameter uncertainty
Weighted average procedure costs based on one province's amalgam procedure statistics, based on the number of surfaces and type of tooth	X	X		To address structural (i.e., unknown natural history of an initial restoration in a child) and parameter uncertainty (i.e., incomplete Canadian data set of procedure fees)
Upper and lower limits of 95% CI for age at initial restoration		X		To address structural uncertainty (i.e., unknown average age at initial restoration in Canada)
0% discounting		X		As per CADTH economic analysis guidelines
5% discounting		X		As per CADTH economic analysis guidelines
Exploratory: crown after 2nd and 3rd restoration failure		X		To address structural uncertainty (i.e., unknown natural history of an initial restoration in a child)
Exploratory: extraction after 3rd restoration failure		X		To address structural uncertainty (i.e., public programs which do not cover crowns and root canal treatments)
Upper and lower limits of 95% CI for procedure time			X	To address parameter uncertainty
Minimum and maximum values for average hourly wages			X	To address parameter and structural uncertainty (i.e., unknown CI)
Upper and lower limits of procedure time multiplier (for composite resin restorations)			X	To address parameter and structural uncertainty (i.e., unknown value and CI)

CI = confidence interval; NECAT = New England Children's Amalgam Trial.

In view of the limited information describing the natural history of a tooth restoration in the medical literature, the base-case model did not take into consideration that in real life, subsequent restorations tend to become larger in size and, after a certain number of replacements, a crown may be the best or most feasible option. To account for this, exploratory scenarios were developed where it was assumed that a crown was placed after the 2nd or 3rd failure, based on feedback from the two clinical experts in dentistry involved in this review (C.Q.: expert opinion, 2017 Dec; S.E.: expert opinion, 2017 Dec). One publication was found on the natural history of a crown.[73] The success rate at 10 years (i.e., latest time point available) was taken from that study.[73] In this scenario, once the crown has failed, the tooth was assumed to be extracted. A variant of this exploratory scenario was performed where the tooth was extracted after the 3rd restoration failure to address the fact that some public programs do not cover crown placement.

Because of a lack of data, planned sensitivity analyses on population subgroups (i.e., children, adults, elderly) and settings (remote, rural, and urban) were not performed. Furthermore, no sensitivity analysis was performed for consequence number 3. The calculations for consequence number 3 were based upon data from the Environmental Impact section, which performed deterministic calculations whereby parameters involved in the calculation had no associated variability.

All inputs and sensitivity analysis parameters are listed in Appendix 10.

Model assumptions

The following assumptions made for this cost-consequence analysis are presented in Table 6.

Table 6: Cost-Consequence Base-Case Model Assumptions

Assumption	Consequence				Justification and Potential Impact on Results
	1	2	3	4	
The two restorative materials studied were assumed to be an equally appropriate treatment option for the tooth to be restored.	X	X	X	X	While in reality there might be situations where one material is preferable over the other, for this analysis we assumed that both restorative materials could be used interchangeably.[64,65]
Two- and three-surface restorations are assumed to represent the most frequently performed restorations in both publicly and privately paid dental services.	X	X			This might be an underestimation of the average restoration size, in particular in public programs. These programs are mostly in place for low-income individuals and families, and epidemiological studies suggest these subpopulations have poorer oral health. The incidence of tooth caries has been shown to be related to income level and access to dental care.[87] This potential underestimation has been addressed in the sensitivity analyses.
The average cost of restoration was calculated by assuming an equal number of two- and three- surface restorations being performed equally on premolar and molars.	X	X			This might be an underestimation of costs, as restorations to molar teeth are likely more frequent as per the opinion of the two clinical experts in dentistry involved in this review (C.Q.: expert opinion, 2017 Aug; S.E.: expert opinion, 2017 Aug). Furthermore, this might result in an overestimation of composite resin restoration costs, as some public programs do not cover composite resin restorations to posterior teeth. This has been addressed in the sensitivity analyses.
Dental fees obtained are assumed to be representative of those jurisdictions in which dental fee lists were not available.	X	X			See sensitivity analyses for alternative cost assumptions.

Assumption	Consequence				Justification and Potential Impact on Results
	1	2	3	4	
Time-to-restoration failure was assumed to be independent of the number of surfaces restored (i.e., 2 and 3 surfaces) or type of tooth (i.e., molar versus premolar).	X	X			The NECAT reported that the size of the restoration had an impact on the time-to-restoration failure. However, no information was available on the relationship between the number of surfaces restored and the time-to-restoration failure. Similarly, no information was found on the relationship between the type of tooth and the time to failure. Multiple sensitivity analyses have been performed to try to address this.
Patient age at the time of the first restoration on a permanent posterior tooth was assumed to be similar to that of the NECAT population; i.e., 7.9-years-old.		X			No information was found on the age of Canadian children at the time of the first restoration to a permanent posterior tooth. However, the two clinical experts in dentistry involved in this review agreed that the value from the NECAT was likely applicable to Canada (C.Q.: expert opinion, 2017 Aug; S.E.: expert opinion, 2017 Aug).
A gender split of 7.9-year-old children was assumed to be equal to that of the 5- to 9-year-old Canadian population.		X			There is no reason to believe that children having a restoration to a permanent posterior tooth would have a different gender split.
The same restoration material was used for subsequent restorations.		X			According to the clinical experts in dentistry consulted in this review, there is a growing trend toward replacing existing amalgam restorations with composite resin (C.Q.: expert opinion, 2017 Aug; S.E.: expert opinion, 2017 Aug). Given the limited data on the proportion of patients switching to composite resin, and the fact that switching would blur the results of the analysis, the model assumed that the same material would be used for all subsequent restoration failures. This was not further tested in the sensitivity analysis.
Subsequent restorations were assumed to fail at the same rate as the initial restoration.		X			Limited information on the natural history of a tooth restoration was found on the time to failure of subsequent dental restorations. It is uncertain if this assumption is close to the reality as one might suspect that, as restoration margins grow in size with replacement, the risk of failure also increases. Alternative time to failure values (i.e., lower and upper level of 95% CI) were used in sensitivity analyses.
Subsequent restorations were assumed to be of the same size as the initial restoration.		X			Limited information on the natural history of a tooth restoration was found on the size of subsequent restoration. This assumption is unlikely to be reflective of the reality, as it is well-accepted that restorations will be larger with subsequent repairs. This is likely to bias the composite resin arm more than the amalgam arm, as composite resin restorations are more expensive and have a shorter time to failure; hence, this assumption might be underestimating the composite resin restoration costs. See the sensitivity analyses for the alternative natural history tested.
Amalgam separator-related costs reported by one dentist are representative of costs throughout Canada.			X		Values reported by the dentist consulted were consistent with information found on the Internet.
Dividing the number of dentists using amalgam by the average number of dentists per clinic gives an adequate representation of the number of dental clinics in Canada that have an amalgam separator.			X		It is unknown how close this assumption is to the reality. As this is used to calculate the costs of amalgam separation, this value may be under- or overestimated.
Procedure time for a composite resin restoration is 15% longer than for an amalgam restoration.				X	No recent information to populate this parameter has been found in the medical literature. It is generally agreed that composite resin restorations take more time, but using this assumption may under- or overestimate the productivity loss with composite resin restorations. The uncertainty around this parameter has been addressed by using a large range of possible values (+5% to +30% longer) in the

Assumption	Consequence				Justification and Potential Impact on Results
	1	2	3	4	
					probabilistic analysis and scenario analyses using the lower and upper values of this range.
Travel time to the dental clinic and waiting time at the dental clinic are assumed to be irrelevant for the purpose of this analysis.				X	Both travel time to the clinic and waiting time at the clinic are not expected to vary with dental restoration material and therefore it is likely appropriate to omit them if one is interested in the incremental difference in productivity between these two procedures.
Productivity lost was based on time off formal work. The averages of the lowest and highest provincial hourly wages were assumed to be a good proxy of the variability of the average Canadian hourly wage and were assumed to represent the lower and upper limits of the 99.7% distribution.				X	Statistics Canada does not report variability of their estimates. This assumption allowed including the average wage in the probability sensitivity analysis. This particular method generated the closest average hourly wage value to the value reported by Statistics Canada.

CI = confidence interval; NECAT = New England Children's Amalgam Trial.

Model validation

Face validity of the model was achieved through consultation with two Canadian clinical experts in dentistry throughout the research phase to ensure that the model was consistent with Canadian practice, that the best available data sources were used, that no significant evidence was omitted, and that results were consistent with their expectations and what is known in the medical literature. Internal validity was ensured by testing extreme parameter values. The model results were compared with other models in the dental field for cross-validity. Where possible, results were compared with other similar estimations for external validity.

Results

Key findings

Given the clinical and non-clinical outcomes that can be affected by the choice of restoration material for a posterior dental restoration, a cost-consequence analysis was performed. Table 7 highlights the key quantitative findings.

Table 7: Key Findings of the Cost-Consequence Analysis

Consequence	Amalgam		Composite Resin	
	Consequence Average (95%CI)	Canadian Total Cost Average (95%CI)	Consequence Average (95%CI)	Canadian Total Cost Average (95%CI)
Time horizon of analysis: Lifespan of first restoration				
1. Useful life of a restoration	132.6 months (101.1 to 164.3)	$171 ($147 to $198)	95.7 months (82.8 to 108.3)	$219 ($188 to $256)
Time horizon of analysis: Patient's lifetime[a]				
2. Lifetime need for replacement	4.0 replacements[b] (3.1 to 4.6)	$686[b] ($508 to $842)	5.7 replacements[b] (4.4 to 6.2)	$1,245[b] ($936 to $1,513)
Time horizon of analysis: 1 year				
3. Hg waste management[cc]	2.51 kg of Hg per year reaching surface water	$16.63 million	Not applicable	Not applicable
Time horizon of analysis: Dental procedure				
4. Productivity loss	From 23.7 min. (10.3 to 47.7) for a two-surface restoration on a premolar to 36.0 min. (17.1 to 66.3) for a three-surface restoration on a molar	$7.17 ($2.64 to $15.52) to $10.91 ($4.47 to $22.49)	From 27.3 min. (11.7 to 55.4) for a two-surface restoration on a premolar to 41.5 min. (19.8 to 76.7) for a three-surface restoration on a molar	$8.26 ($3.03 to $18.10) to $12.25 ($5.85 to $22.64)

CI = confidence interval; Hg = mercury; min.= minutes.

NOTE: All analyses are probabilistic unless otherwise specified.

[a] Assuming a patient age similar to the NECAT (mean age: 7.9 years; gender: 51% male)

[b] 1.5% discounted

[c] Deterministic analysis

Details on each consequence follow.

Consequence number 1 – Useful life of a restoration

Base-case analysis

When a Weibull distribution was fitted to the survival data on restoration replacement rates from the NECAT, the average time to failure was estimated at 132.5 ± 16.2 months (11.0 ± 1.4 years) for amalgam restorations and 95.8 ± 6.5 months (8.0 ± 0.5 years) for composite resin restorations.[67] Figure 3 shows the results of the curve fitting and extrapolation of the time-to-restoration failure based on the data from the NECAT.

Table 8 shows the results of the expected lifespan and cost for the initial restoration, based on 5,000 probabilistic iterations.

Figure 3: Curve Fitting and Extrapolation of Time-to-Restoration Failure From the NECAT Data

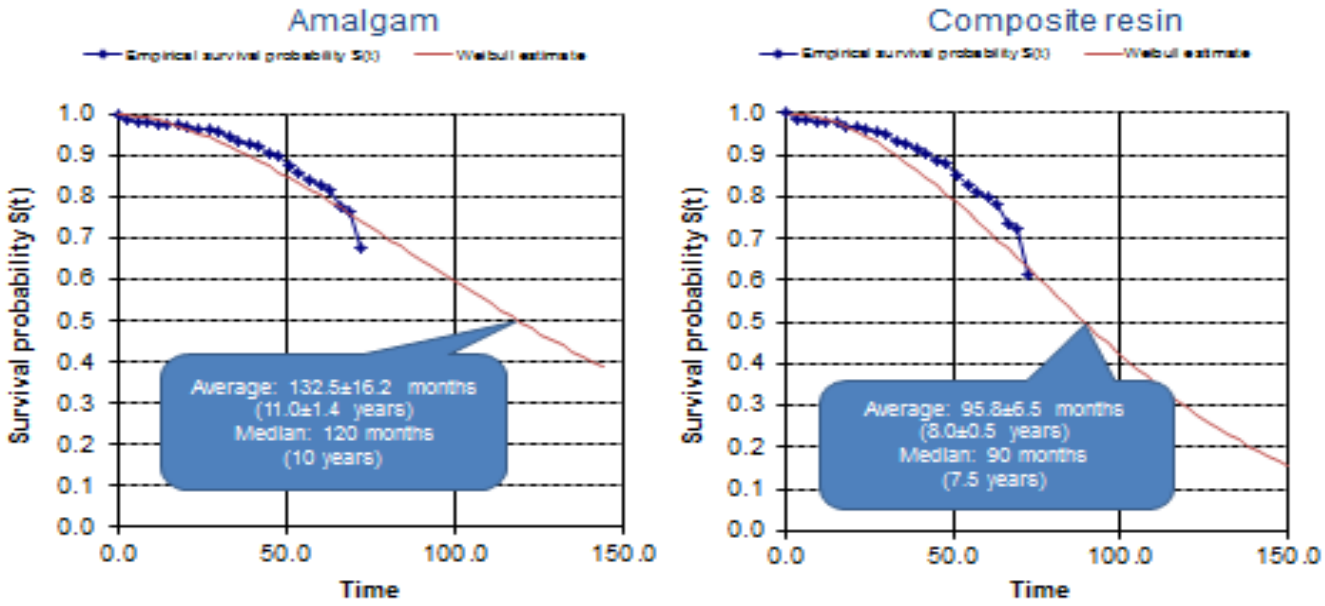


Table 8: Posterior Teeth Restoration Costs and Useful Time (Probabilistic Analysis)

		Amalgam Average (95%CI)	Composite Resin Average (95%CI)	Difference (Composite Resin — Amalgam)
Consequence	Useful life (months)	132.6 (101.1, 164.3)	95.7 (82.8, 108.3)	–36.9
Cost of restoration	Canadian, public:private mix: 5.5:94.5	$171 ($147, $198)	$219 ($188, $256)	$49
	Private only	$172 ($148, $201)	$221 ($189, $260)	$49
	Public only	$134 ($85, $200)	$186 ($122, $272)	$52

CI = confidence interval.

Sensitivity analyses

As noted previously, the clinical review identified another study, Casa Pia, which was considered less generalizeable to the Canadian setting. A sensitivity analysis was planned with the data from this study. The Casa Pia study reported restoration failure differently than the NECAT; i.e., due to secondary caries (the vast majority of failures) and due to restoration/tooth fracture separately.[70] Fitting a Weibull distribution to the survival curve on years since restoration due to secondary caries and extrapolating gave an estimated average time to failure of 1,288.0 ± 146.3 months (107.3 ± 12.2 years) for amalgam restorations and 903.5 ± 130.8 months (75.3 ± 10.9 years) for composite resin restorations. After discussion with the clinical experts in dentistry involved in this review, it was felt that these results were neither realistic nor clinically meaningful (C.Q.: expert opinion, 2017 Nov; S.E.: expert opinion, 2017 Nov). Therefore the sensitivity analysis using the Casa Pia study

was not performed. The curve fitting figures from the Casa Pia study can be found in Appendix 10.

All other scenario and sensitivity analyses described in Table 5 were performed as planned. Results were robust to sensitivity analyses and are displayed in Table 9. Using the lower and upper limits of the 95% CI of the time to failure had little impact on the estimated useful life of both amalgam and composite resin restorations. All scenarios resulted in composite resin restorations being $42 to $56 more expensive than amalgam restorations despite a useful life of approximately 36 months (three years) shorter.

Table 9: Consequence Number 1 Scenario and Sensitivity Analyses

	Amalgam		Composite Resin		Difference (Composite Resin — Amalgam)	
	Useful Life (Months) Average (95% CI)	Costs Average (95% CI)	Useful Life (Months) Average (95% CI)	Costs Average (95% CI)	Useful Life (Months)	Costs
Canadian (private:public mix) perspective						
Base case	132.6 (101.1, 164.3)	$171 ($147, $198)	95.7 (82.3, 108.3)	$219 ($188, $256)	–36.9	$49
Extreme value analysis: smallest time-to-failure difference between groups	131.0 (98.7, 163.2)	$173 ($147, $201)	96.2 (83.4, 108.9)	$222 ($187, $262)	–34.8	$49
Extreme value analysis: largest time-to-failure difference between groups	133.9 (102.3, 165.6)	$173 ($147, $201)	95.2 (82.8, 108.0)	$221 ($187, $261)	–38.7	$49
Average of all surfaces restoration costs	132.2 (99.6, 163.9)	$191 ($120, $288)	95.7 (82.8, 108.9)	$247 ($161, $370)	–36.5	$56
Weighted average procedure costs based on one province's amalgam procedure statistics on size of surface restored	132.6 (101.9, 164.1)	$157 ($99, $237)	95.8 (83.0, 108.3)	$199 ($130, $289)	–36.8	$42

CI=confidence interval.

Consequence number 2 – Lifetime need for replacement

The patient-level simulation estimated that, with an average time to failure of 11.0 ± 1.4 years for an amalgam restoration, an average of 7.8 (95%CI, 5.0 to 9.0) restorations would be performed on a tooth restored with amalgam when the initial restoration is done in a 7.9-year-old child (1.5% discounted: 4.0 restorations; 95%CI, 3.1 to 4.6). If composite resin is used, assuming an average time to failure of 8.0 ± 0.5 years, an average of 10.7 (95%CI, 7.0 to 12.0) restorations would be needed on the initial restoration in a child of the same age (1.5% discounted average: 5.7; 95%CI, 4.4 to 6.2). Lifetime discounted costs in the Canadian perspective would be $686 (95%CI, $508 to $842) for amalgam restorations and

$1,245 (95%CI, $936 to $1,513) for composite resin restorations. Assuming a 1.5% discount rate, 1.7 additional replacements for composite restorations (2.9, undiscounted) would be needed and would result in an additional lifetime discounted cost of around $560 ($1,024, undiscounted). Results for the private and public perspectives are shown inTable 10.

Table 10: Lifetime Restoration Replacements and Costs

	Amalgam Average (95%CI)	Composite Resin Average (95% CI)	Difference (Composite Resin — Amalgam)
Number of restoration replacements — undiscounted	7.8 (5.0 to 9.0)	10.7 (7.0 to 12.0)	2.9
Number of restoration replacements — 1.5% annual discount rate	4.0 (3.1 to 4.6)	5.7 (4.4 to 6.2)	1.7
Lifetime costs — 1.5% discounted			
Canadian (public:private mix — 5.5:94.5)	$686 ($508 to $842)	$1,245 ($936 to $1,513)	$560
Private	$694 ($515 to $855)	$1,257 ($936 to $1,535)	$562
Public	$538 ($325 to $824)	$1,053 ($647 to $1,578)	$515
Lifetime costs — undiscounted			
Canadian (public:private mix — 5.5:94.5)	$1,329 ($841 to $1,713)	$2,353 ($1,474 to $2,984)	$1,024
Private	$1,346 ($854 to $1,745)	$2,375 ($1,483 to $3,032)	$1,029
Public	$1,044 ($557 to $1,655)	$1,990 ($1,095 to $3,057)	$946

CI=confidence interval.

Sensitivity Analysis

Similar to consequence number 1, the planned sensitivity analysis using the data from the Casa Pia study was not performed, as the curve fitting led to estimates of average time to failure that were not felt to be realistic. Results from all other sensitivity analyses specified in Table 5 are presented in Consequence Number 2 Scenario and Sensitivity Analyses (Table 11) and the results are in line with the base-case results; i.e., one to three additional restoration replacements with composite resin for additional discounted costs around $500 to $600. The 5% discounting scenario gave the smallest difference between composite resin and amalgam while at the same time assuming that a 0% discounting gave the largest difference.

Table 11: Consequence Number 2 Scenario and Sensitivity Analyses

	Amalgam		Composite Resin		Difference (Composite Resin — Amalgam)	
	Discounted Number of Restoration Replacements (95% CI)	Discounted Costs Average (95% CI)	Discounted Number of Restoration Replacements (95% CI)	Discounted Costs Average (95% CI)	Number of Restoration Replacements	Costs
Canadian (private:public mix) perspective						
Base case	4.0 (3.1 to 4.6)	$686 ($508 to $842)	5.7 (4.4 to 6.2)	$1,245 ($936 to $1,513)	1.7	$560
Extreme value analysis: smallest time-to-failure difference between groups	4.1 (3.2 to 4.7)	$694 ($524 to $856)	5.6 (4.5 to 6.2)	$1,239 ($936 to $1,507)	1.6	$545
Extreme value analysis: largest time-to-failure difference between groups	4.0 (3.1 to 4.5)	$677 ($510 to $834)	5.7 (4.5 to 6.2)	$1,249 ($960 to $1,506)	1.7	$572
Average of all surface restoration costs	4.0 (3.1 to 4.6)	$767 ($454 to $1,178)	5.7 (4.5 to 6.2)	$1,386 ($864 to $2,036)	1.6	$620
Weighted average procedure costs based on province's amalgam procedure statistics on size of surfaces restored	4.0 (3.1 to 4.6)	$617 ($368 to $943)	5.7 (4.5 to 6.2)	$1,119 ($689 to $1,660)	1.7	$502
Lower limit of 95% CI for age at initial restoration (age = 7.8 years)	4.0 (3.1 to 4.6)	$688 ($512 to $849)	5.7 (4.5 to 6.2)	$1,249 ($962 to $1,513)	1.7	$561
Upper limit of 95% CI for age at initial restoration (age = 8.0 years	4.0 (3.1 to 4.6)	$686 ($513 to $849)	5.7 (4.5 to 6.2)	$1,249 ($960 to $1,505)	1.7	$563
0% discounting	7.8 (5.0 to 9.0)	$1,329 ($841 to $1,713)	10.7 (7.0 to 12.0)	$2,353 ($1,474 to $2,984)	2.9	$1,024

	Amalgam		Composite Resin		Difference (Composite Resin — Amalgam)	
	Discounted Number of Restoration Replacements (95% CI)	Discounted Costs Average (95% CI)	Discounted Number of Restoration Replacements (95% CI)	Discounted Costs Average (95% CI)	Number of Restoration Replacements	Costs
5% discounting	1.4 (1.2 to 1.6)	$236 ($187 to $295)	2.1 (1.9 to 2.2)	$453 ($373 to $541)	0.7	$217

CI=confidence interval.

The scenario where a crown was installed after the third restoration failure led to expected costs that were similar to the base case in the amalgam group (i.e., $689 versus $686 in the base case) but lowered the expected cost in the composite resin group (i.e., $986 versus $1,245 in the base case). One important difference between restoration materials in the lifetime analysis is the time at which the costs are incurred. This is illustrated for the crown scenario in Table 12 which shows that lifetime undiscounted costs are slightly higher and happen earlier with composite resin than with amalgam. Other important differences are the time at which a crown is installed and the time at which the tooth is extracted. In the crown at the third failure scenario, a crown was estimated to be installed once an individual reaches an average of 41.0-years-old when the initial restoration was made of amalgam compared to 31.8-years-old if the initial restoration was made with composite resin. The tooth would be extracted in 22% of individuals at an average age of 48.4-years-old with amalgam and 39.3-years-old with composite resin. In comparison, in the crown at second failure, crown placement and/or extraction, occur about 10 years earlier. In both of these scenarios, the bulk of the costs are from crown placement. Table 12 also shows a variant of the crown scenario for public programs that do not cover crown placement, in which it was assumed that the tooth would be extracted following the third restoration failure. This scenario resulted in the lowest cost estimates of all scenarios analyzed. However, the patient would lose their tooth at an average age of 41.1-years-old with amalgam compared to 31.9-years-old with composite resin.

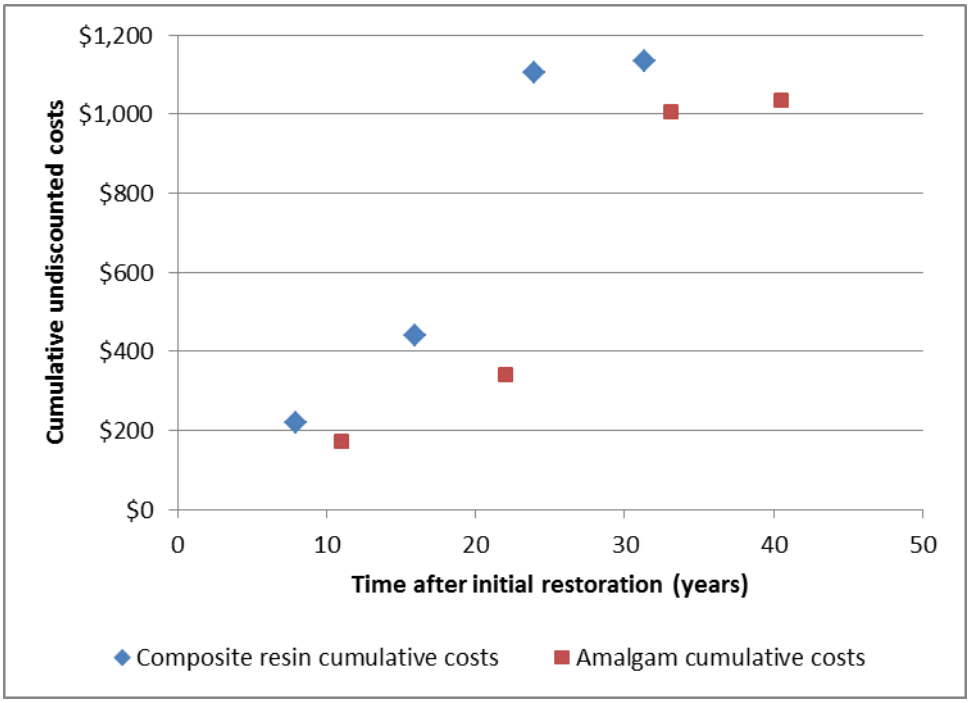
Table 12: Result of Scenario Analyses With Crown

	Amalgam	Composite Resin
Crown at 2nd failure		
Total number of failures (n, 95%CI)	2.2 (2.0, 3.0)	2.2 (2.0, 3.0)
Restoration failures	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)
Crown failures	0.2 (0.0, 1.0)	0.2 (0.0, 1.0)
Lifetime 1.5% discounted costs (average, 95%CI)		
Canadian	$639 ($371, $1,088)	$737 ($439, $1,223)
Private	$644 ($361, $1,119)	$742 ($430, $1,254)
Public	$537 ($290, $967)	$650 ($368, $1,128)
Canadian undiscounted costs (average, 95%CI)	$859 ($484, $1,473)	$910 ($530, $1,532)
Restoration costs	$171 ($146, $197)	$220 ($187, $257)
Crown costs (excluding laboratory fees)	$661 ($301, $1,274)	$662 ($301, $1,274)
Extraction costs	$27 ($0, $133)	$29 ($0, $133)
Age at crown (average, 95%CI)	30.0 (25.4, 34.5)	23.9 (20.7, 27.0)

	Amalgam	Composite Resin
Age at extraction (average, 95% CI)	37.5 (31.0, 45.7)	31.2 (25.8, 39.3)
Crown at 3rd failure		
Total number of failures (n, 95%CI)	3.2 (3.0, 4.0)	3.2 (3.0, 4.0)
Restoration failures	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Crown failures	0.2 (0.0, 1.0)	0.2 (0.0, 1.0)
Lifetime 1.5% discounted costs (average, 95%CI)		
Canadian	$689 ($457, $1,053)	$852 ($588, $1,264)
Private	$696 ($453, $1,078)	$859 ($581, $1,290)
Public	$582 ($349, $936)	$740 ($464, $1,148)
Canadian undiscounted costs (average, 95%CI)	$1,035 ($661, $1,635)	$1,133 ($754, $1,712)
Restoration costs	$341 ($293, $392)	$439 ($374, $510)
Crown costs (excluding laboratory fees)	$665 ($311, $1,248)	$665 ($312, $1,248)
Extraction costs	$29 ($0, $135)	$29 ($0, $134)
Age at crown (average, 95%CI)	41.0 (35.8, 46.2)	31.8 (28.6, 35.1)
Age at extraction (average, 95% CI)	48.4 (41.3, 56.9)	39.3 (33.9, 46.2)
Extraction at 3rd failure		
Total number of failures (n, 95%CI)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Restoration failures	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Lifetime 1.5% discounted costs (average, 95%CI)		
Public	$273 ($193, $380)	$384 ($271, $529)
Public undiscounted costs (average, 95%CI)	$367 ($263, $507)	$472 ($316, $680)
Restoration costs	$270 ($174, 401)	$374 ($244, $546)
Extraction costs	$101 ($63, $152)	$101 ($63, $152)
Age at extraction (average, 95%CI)	41.1 (35.8, 46.4)	31.9 (28.5, 35.3)

CI = confidence interval; n = number.

Figure 4: Cumulative Undiscounted Costs Over Time (Crown After Third Failure Scenario)



Consequence number 3 — Mercury waste

According to the calculations performed in the environmental section of this report, it is estimated that a total of 1,848 kg of mercury — through amalgam placement (292.9 kg) and removal (1,555 kg) — flows into the waste water systems of dental clinics in Canada each year. Of that, most of it would be captured by chairside traps and amalgam separators, leaving 30.3 kg per year to be discharged into the sewage system. Some of it would later be captured by waste water treatment plants. Thus, it is estimated that dentistry contributes 2.51 kg (including 1.0 kg from the incineration of dental clinic biosolids) out of the total of 4,470 kg of Hg that reaches Canadian surface waters each year.

The annualized cost of amalgam separators (acquisition, installation, operation, and maintenance) was estimated at $2,498. As per the environmental section, it is estimated that 13,232 general practitioners and 750 specialist dentists use amalgam in their practices. Using 2.1 as the average number of dentists per clinic means that there are roughly 6,658 dental clinics in Canada.[83] As each clinic requires one amalgam separator, it is estimated that approximately $16,634,696 is spent each year in Canada by dental practices on amalgam separators overall. Results for consequence number 3 are displayed in Table 13.

Table 13: Mercury Waste and Management Costs

Hg Waste Produced by Dental Clinics			Hg Waste Management Costs	
Number of Canadian dentists using amalgam	13,982		Number of Canadian dentists using amalgam	13,982
General practitioners	*13,232*		*General practitioners*	*13,232*
Specialists	*750*		*Specialists*	*750*
Amount of Hg waste from dental restorations	1,847.9 kg		*Average number of dentists per clinic*	2.1
From amalgam placement	*292.9 kg*		*Average number of dental clinics*	6,658
From amalgam removal	*1,555 kg*		Average annual amalgam separator costs (calculated over 5 years; discount rate: 1.5%)	$2,498
Amount of Hg waste captured by chairside traps and amalgam separators	1,818 kg		Annual costs for Canadian dental clinics	$16.6 million
Amount captured by waste water treatment plants	28.7 kg			
Amount of Hg waste reaching surface waters	2.51 kg			
From waste waster	*1.51 kg*			
From incineration of biosolid	*1.0 kg*			

Hg = mercury; kg = kilogram.

Consequence number 4 — Productivity loss

The procedure time for two- and three-surface restorations in premolars and molars was estimated to range between 23.7 minutes (95% CI, 10.3 to 47.7) for a two-surface amalgam restoration on a premolar to 41.5 minutes (95% CI, 19.8 to 76.7) for a three-surface composite resin restoration on a molar. Additional details can be found in Table 14.

Table 14: Estimated Average (95% CI) Procedure Times in Minutes per Restoration Material, Number of Surfaces Restored and Tooth Type (Probabilistic Analysis)

Surfaces Restored	Amalgam Average Procedure Time in Minutes (95%CI)		Composite Resin Average Procedure Time in Minutes (95%CI)		Difference in Minutes (Composite Resin — Amalgam)	
	Premolar	Molar	Premolar	Molar	Premolar	Molar
2-surface restoration	23.7 (10.3 to 47.7)	29.7 (12.9 to 59.9)	27.3 (11.7 to 55.4)	34.2 (14.8 to 69.6)	3.6	4.5
3-surface restoration	28.1 (13.4 to 51.8)	36.0 (17.1 to 66.3)	32.4 (15.4 to 59.6)	41.5 (19.8 to 76.7)	4.3	5.5

CI = confidence interval.

Using an average hourly wage of $26.96 (minimum: $13.19, maximum: $46.38) and 65.7% as the proportion of the population in the workforce, the productivity loss was estimated to vary between $7.17 (95% CI, $2.64 to $15.52) for a two-surface amalgam restoration of a premolar to $12.25 (95% CI, $5.85 to $22.64) for a three-surface composite resin restoration of a molar. Further details are given in Table 15. Thus, a composite restoration requires between 3.6 to 5.5 additional minutes to perform and generates less than $2 in productivity loss.

Table 15: Estimated Average (95% CI) Productivity Loss per Restoration Material, Number of Surfaces Restored and Tooth Type — Individual With One Restoration Only (Probabilistic Analysis)

Number of Surfaces	Amalgam Average (95%CI)		Composite Resin Average (95%CI)		Difference (Composite Resin — Amalgam)	
	Premolar	Molar	Premolar	Molar	Premolar	Molar
2-surface	$7.17 ($2.64, $15.52)	$9.00 ($3.32, $19.49)	$8.26 ($3.03, $18.10)	$10.36 ($3.78, $22.54)	$1.09	$1.36
3-surface	$8.52 ($3.49, $17.56)	$10.91 ($4.47, $22.49)	$9.56 ($4.55, $17.60)	$12.25 ($5.85, $22.64)	$1.04	$1.34

CI = confidence interval.

Sensitivity analyses on the procedure times and hourly wages as specified in Table 5 are displayed in Table 16. The sensitivity analyses showed that the incremental time loss could be as low as 1.2 minutes for a two-surface premolar to as high as 10.9 minutes for a three-surface premolar. Consequently, incremental productivity loss could be as low as $0.51 to as high as $2.89.

Table 16: Consequence Number 7 Scenario and Sensitivity Analyses

Scenario		Amalgam		Composite Resin		Difference (Composite Resin — Amalgam)	
Number of Surfaces	**Consequence**	**Premolar Average (95%CI)**	**Molar Average (95%CI)**	**Premolar Average (95%CI)**	**Molar Average (95%CI)**	**Premolar**	**Molar**
Lower limit of amalgam procedure time							
2-surface	Time loss (minutes): 2-surface	11.1 (4.7 to 22.9)	14.0 (6.0 to 28.7)	12.8 (5.4to 26.4)	16.1 (6.8 to 32.8)	1.7	2.1
	Productivity loss: 2-surface	$3.37 ($1.25 to $7.40)	$4.23 ($1.56 to $9.29)	$3.88 ($1.44 to $8.48)	$4.87 ($1.80 to $10.66)	$0.51	$0.64
3-surface	Time loss (minutes): 3-surface	14.7 (7.3 to 26.7)	18.8 (9.4 to 34.2)	16.9 (8.4 to 30.9)	21.7 (10.8 to 39.5)	2.2	2.8
	Productivity loss: 3-surface	$4.46 (1.87 to $9.26)	$5.71 ($2.39 to $11.87)	$4.99 ($2.47 to $9.12)	$6.39 ($3.18 to $11.65)	$0.53	$0.68
Upper limit of amalgam procedure time							
2-surface	Time loss (minutes): 2-surface	45.7 (19.1 to 92.4)	57.4 (24.0 to 116.0)	52.7 (21.8 to 105.4)	66.1 (27.5 to 133.2)	6.9	8.7
	Productivity loss: 2-surface	$13.82 ($5.17 to $30.69)	$17.36 ($6.49, $38.53)	$15.91 ($5.91 to $35.28)	$19.99 ($7.49 to $44.55)	$2.09	$2.63
3-surface	Time loss (minutes): 3-surface	55.8 (27.4 to 101.1)	71.5 (35.0 to 129.5)	64.2 (31.4 to 115.9)	82.3 (40.1 to 148.9)	8.4	10.8
	Productivity loss: 3-surface	$16.85 ($7.18 to $33.91)	$21.59 ($9.19 to $43.44)	$18.95 ($9.27 to $34.19)	$24.28 ($11.85 to $43.92)	$2.10	$2.70
Lower limit of hourly wages							
2-surface	Time loss (minutes): 2-surface	23.6 (10.1 to 46.3)	29.7 (12.7 to 58.1)	27.2 (11.6 to 53.6)	34.3 (14.5 to 67.8)	3.6	4.5
	Productivity loss: 2-surface	$3.50 ($1.30 to $7.59)	$4.39 ($1.63 to $9.53)	$4.03 ($1.50 to $8.75)	$5.06 ($1.88 to $11.11)	$0.53	$0.67
3-surface	Time loss (minutes): 3-surface	28.2 (14.0 to 50.6)	36.1 (17.9 to 64.8)	32.5 (15.9 to 58.3)	41.6 (20.6 to 75.3)	4.3	5.5
	Productivity loss: 3-surface	$4.18 ($1.76 to $8.50)	$5.35 ($2.26 to $10.89)	$4.69 ($2.30 to $8.41)	$6.01 ($2.97 to $10.88)	$0.51	$0.65

Scenario		Amalgam		Composite Resin		Difference (Composite Resin — Amalgam)	
Number of Surfaces	**Consequence**	**Premolar Average (95%CI)**	**Molar Average (95%CI)**	**Premolar Average (95%CI)**	**Molar Average (95%CI)**	**Premolar**	**Molar**
Upper limit of hourly wages							
2-surface	Time loss (minutes): 2-surface	23.6 (10.1 to 47.8)	29.7 (12.7 to 60.0)	27.2 (11.6 to 54.6)	34.1 (14.5 to 68.8)	3.5	4.4
	Productivity loss: 2-surface	$12.28 ($4.53 to $27.13)	$15.41 ($5.69 to $34.07)	$14.11 ($5.17 to $31.43)	$17.73 ($6.55 to $39.21)	$1.84	$2.31
3-surface	Time loss (minutes): 3-surface	28.3 (13.9 to 52.0)	36.3 (17.8 to 66.7)	32.6 (15.8 to 60.3)	41.7 (20.0 to 77.1)	4.2	5.4
	Productivity loss: 3-surface	$14.66 ($6.11 to $29.81)	$18.78 (7.83 to $38.18)	$16.53 ($8.01 to $30.60)	$21.17 ($10.17 to $39.15)	$1.86	$2.39
Lower limit of time procedure ratio							
2-surface	Time loss (minutes): 2-surface	23.7 (10.2 to 42.7)	29.8 (12.8 to 59.2)	24.9 (10.6 to 49.3)	31.3 (13.3 to 62.5)	1.2	1.5
	Productivity loss: 2-surface	$7.18 ($2.61 to $15.64)	$9.02 ($3.27 to $19.63)	$7.55 ($2.75 to $16.38)	$9.48 ($3.47 to $20.85)	$0.36	$0.47
3-surface	Time loss (minutes): 3-surface	28.1 (14.0 to 51.5)	36.0 (17.9 to 66.0)	29.5 (14.7 to 54.1)	37.9 (18.7 to 68.8)	1.4	1.8
	Productivity loss: 3-surface	$8.50 ($3.65 to $17.25)	$10.88 ($4.67 to $22.09)	$8.72 ($4.33 to $15.95)	$11.18 ($5.51 to $20.29)	$0.22	$0.29
Upper limit of time procedure ratio							
2-surface	Time loss (minutes): 2-surface	23.6 (10.0 to 47.6)	29.7 (12.5 to 59.8)	30.7 (13.0 to 62.1)	38.6 (16.1 to 78.1)	7.1	8.9
	Productivity loss: 2-surface	$7.18 ($2.62 to $15.76)	$9.01 (3.29 to $19.79)	$9.34 ($3.42 to $20.55)	$11.73 ($4.24 to $25.87)	$2.16	$2.71
3-surface	Time loss (minutes): 3-surface	28.2 (13.8 to 51.0)	36.1 (17.7 to 65.3)	36.7 (17.8 to 66.5)	47.0 (22.9 to 84.5)	8.5	10.9
	Productivity loss: 3-surface	$8.56 ($3.57 to $17.30	$10.97 ($4.57 to $22.16)	10.82 ($5.25 to $19.63)	$13.86 ($6.76 to $24.92)	$2.26	$2.89

CI = confidence interval.

Summary of Results

A cost-consequence model was deemed to be more appropriate for the economic analysis comparing the amalgam and composite resin restorations of permanent posterior teeth. Seven consequences were originally identified, but, because of a lack of evidence to allow modelling, three of the seven consequences were excluded, leaving the following consequences evaluated in the economic analysis: useful life of a restoration, lifetime need for restoration replacement, annual waste management, and productivity loss during restoration.

Using the NECAT, the useful life of an amalgam restoration for a permanent posterior tooth was estimated to be 11.0 ± 1.4 years at an estimated average Canadian cost of $171 (95%CI, $147 to $198) compared to 8.0 ± 0.5 years at an estimated average Canadian cost of $219 (95%CI, $188 to $256) for a composite resin restoration, assuming a two- or three-surface restoration.

As time to failure is longer with amalgam restorations, an average of 7.8 replacements (95% CI, 5.0 to 9.0) would be needed on an initial amalgam restoration compared to 10.7 replacements for an initial composite resin restoration (95% CI, 7.0 to 12.0) throughout the lifetime of a 7.9-year-old child (discounted values: 4.0 and 5.7 for amalgam and composite resin, respectively).This assumed that all subsequent failures would be managed identically to the initial tooth restoration. Lifetime discounted Canadian costs were estimated to be $686 (95%CI, $508 to $842) for amalgam restorations compared to $1,245 (95%CI, $936 to $1,513) for composite resin restorations. This was found to be consistent with an evaluation from the Conseil d'évaluation des technologies de la santé du Québec performed in 1997. In that report, it was estimated that lifetime costs with composite resin would be twice that of amalgam.[88] Similarly, a previous estimation of lifetime dental restoration costs in the UK (1997 £) ranged from £303.70 when the initial restoration was made of amalgam to £709.85 when the initial restoration was made of composite resin.[89] Of note, none of these estimations used discounting. In comparison, our estimated undiscounted costs were $1,329 for amalgam and $2,353 for composite resin in the base case. Our findings that lifetime costs with composite resins are double that of amalgam were consistent with the published literature.

In addition, a variety of scenario analyses were conducted under the lifetime need for replacement analysis given the paucity of long-term data describing the management of a dental restoration failure. In assuming that the third restoration failure would result in a crown procedure, undiscounted costs were $1,035 and $1,133 for amalgam and composite resin respectively. No information has been found on the average age at crown placement or tooth extraction in Canada. However, a study in the US showed that 64% of the patients with a crown were greater than 55 years compared to our estimate of 48.4 years old for the amalgam group of the crown at the third failure scenario.[73] The younger average age to crown placement in our analysis may be partly due to the modelled population (i.e., average age at first (initial) restoration: 7.9-years-old) or the simplifying assumption that a crown would be placed at the third restoration failure. The lifetime analysis, despite its limitations, does highlight that, although costs are similar between the two groups, composite resin restoration may lead to requiring a crown placement at a younger age, as time to initial and subsequent restoration failures would be shorter than with amalgam restorations. Requiring a crown sooner may also mean more crowns redone in the patient's lifetime, with a potentially higher risk for the need for root canal treatment, although this was not explicitly

modelled. No published information was found regarding the average age at tooth extraction. The only information found was from the oral health component of the 2007-2009 Canadian Health Measures Survey, which reported that adults between 40- and 59-years-old had an average of 2.42 (95% CI: 2.08 to 2.75) teeth missing and that missing teeth are 50% more frequent in individuals covered by a public program (the target population for the tooth extraction scenario).[66] Nonetheless, caution is required in interpreting the results from this consequence given the number of simplifying assumptions required because of the limited data on the natural history of subsequent replacements following a failed restoration.

It is estimated that amalgam restorations contribute 2.51 kg out of a total of 4,470 kg of Hg that reach Canadian surface waters each year. Amalgam separators have been instrumental in reducing the amount of Hg discharged into waste water by dentists. This has been achieved at an estimated total annual cost of $16.63 million for Canadian dental clinics.

Finally, more time is needed to perform a composite resin restoration, mainly because of the need for stepwise polymerization of the resin.[90] Using dental procedure time as a proxy for patient and caregiver time loss, time loss was estimated to vary between 23.7 minutes (95%CI, 10.3 to 47.7) and 36.0 minutes (95% CI, 17.1 to 66.3) for amalgam restorations, and between 27.3 minutes (95%CI, 11.7 to 55.4) and 41.5 minutes (95%CI, 19.8 to 76.7) for the composite resin restoration of a posterior tooth. Using the average Canadian hourly wage, productivity loss was estimated to vary between $7.17 (95% CI, $2.64 to $15.52) and $10.91 (95%CI, $4.47 to $22.49) for an amalgam restoration, and between $8.26 (95% CI, $3.03 to $18.10) and $12.25 (95%CI, $5.85 to $22.64) for a composite restoration for two-surface premolar and three-surface molar restorations, respectively. Hence, it is estimated that composite resin restorations of the posterior teeth would take between 3.6 to 5.5 additional minutes to perform depending on the size of the restoration and type of tooth; this would generate an incremental productivity loss of under $2 per restoration. Although these numbers do not take into account the time required to reach the dentist‘s office and the waiting time at the dentist’s office, travel and wait time is not expected to vary according to the restoration material used. Therefore, using procedure time may be a sufficient proxy to estimate the difference in productivity lost between restoration materials. Of note, the time to remove a composite resin restoration might be longer due to the bonding used and the colour needing to be similar to the tooth. Hence, the results in lost productivity cannot be generalized to subsequent dental restorations. In the oral health component of the most recent Canadian health survey, more than one-third of respondents reported taking an average of 3.54 hours (95%CI, 3.23 to 3.86) for dental check-ups or problems with their teeth.[66] The estimate includes more than just tooth restoration (e.g., oral exam, imaging, oral hygiene, prevention, etc.) and did not report time loss separately for different methods of dental restoration.

This analysis shows that, on average, amalgam restorations have a longer useful life and cost less. Furthermore, given the longer life of an amalgam restoration, the exploratory analysis indicated that a crown or tooth extraction would occur later in a patient’s life than if composite resin was used. Although a composite resin restoration takes slightly more time to perform, the impact on patient or caregiver productivity is minimal. On the other hand, using amalgam for posterior tooth restoration requires dental clinics to be equipped with amalgam separators to avoid Hg waste from reaching Canadian surface waters. These have significant costs to dental clinics, but these costs are likely already factored into the dental fees, as dental clinics have been using amalgam separators for several years.

Patients' Perspectives and Experiences Review

The objective of this SR was to understand patients' experiences and perspectives on the use of amalgam or composite resin restorations, as well as that of their parents and caregivers. The specific review question was: What are the perspectives and experiences of patients (adults or children), parents of child patients, or caregivers around dental amalgam and composite resin restorations?

Methods

Literature search

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print, In-Process records and daily updates, via Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and Scopus. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dental amalgams and composite resins.

Methodological filters were applied to limit retrieval to qualitative studies or studies relevant to patient perspectives. Retrieval was not limited by publication year or language. See Appendix 2 for the detailed search strategy.

One search for qualitative studies was completed on June 8, 2017 and a separate search for studies describing patient perspectives was completed on July 20, 2017. Regular alerts were established to update the searches until February 1, 2018.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Selection criteria

Eligible studies were primary English-language qualitative studies and mixed-methods studies, with separate reporting of a qualitative component and participant voice data that addressed the review question. Only the qualitative components of mixed-methods studies were eligible. The quantitative component of mixed-methods studies were ineligible, as were studies based on quantitative data or following a quantitative design, including surveys. For the purpose of this review, qualitative studies were studies that focused on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, action research, and feminist research. Studies that have multiple publications using the same data set were included if they reported on distinct research questions; duplicate publications using the same data with the same findings were excluded. To be eligible, studies must have explored or assessed participants' own perspectives directly, not indirectly (i.e., through another person). Table 17 describes the eligibility criteria used in this review.

Table 17: Inclusion Criteria

Population	Patients (adults or children) with experiences or perspectives on dental amalgam and composite resin restorations
Phenomenon of Interest	• The patients' perspectives on and experience with the use of mercury or amalgam for dental restoration compared with the use of composite resin restoration for either themselves or their children • The patients' perspectives on and experience with the use of composite resins for dental restoration for either themselves or their children • The patients' perspectives on and experience with the use of mercury or amalgam for dental restoration for either themselves or their children
Context	The persons' sense of their own well-being or the well-being of their children in relation to the choice of dental restoration material (amalgam or composite resins).
Study Design	Studies that focused on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, action research, and feminist research. Mixed-methods studies were included if these studies had a qualitative component and participant voice data that addressed this review question.

Selection method

Citations were screened by two independent reviewers using the Covidence data management software[91] in accordance with the criteria outlined in Table 17. The process of screening entailed two phases. First, the full set of citations was screened based on title and abstract (if available). Following that, potentially eligible citations were screened based on full-text reading. Any discrepancies were resolved by consultation with a third reviewer.

The final set of studies were exported from Covidence and imported into SUMARI — the JBI software designed to manage the process of evidence synthesis.[92] The SUMARI software houses the templates for critical appraisal and data extraction, and stores the studies included in the review, facilitating the process of evidence synthesis (either meta-analysis or meta-synthesis). In this review, we conducted a meta-synthesis of the qualitative evidence.

Quality assessment

Qualitative papers selected for retrieval were assessed by two independent reviewers for methodological quality using the JBI Qualitative Assessment and Review Instrument (JBI-QARI).[93] Standardized criteria assess congruity between philosophical perspectives, research questions, research methods used, and results reported, as well as the potential influence of the researcher on the research, adequate representation of participants' voices, and whether conclusions flow from the data and the analysis. Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer. No studies were excluded based on an assessment of methodological quality.

Data extraction

Both descriptive study data and study results were extracted from papers included in the review by two independent reviewers using the standardized data extraction tool from JBI-QARI. The extracted data were stored in the QARI software and included specific details about the interventions, populations, study methods, and results of significance to the review question objectives. These descriptive data were summarized and presented in a table of characteristics of included studies.

Data analysis methods

Primary research of qualitative evidence typically generates one or more themes that reflect the participants' voices on the topic. Results that relate to this SR question were extracted from the included study reports. These qualitative research results, called findings in the JBI methodology of synthesis, were pooled using JBI-QARI[93] into a set of relevant themes. The process of pooling involves the aggregation or synthesis of findings to generate a set of statements that represent that aggregation, through assembling the findings rated according to their quality, and categorizing these findings on the basis of similarity in meaning.[94] The question "What is the essence of meaning that each finding represents?" guides the aggregative process and helps the team generate the categories. These categories were then subjected to a meta-synthesis to produce a single comprehensive set of synthesized findings that can be used as a basis for evidence-based practice.

Results

The search strategy located 1,800 citations (PRISMA diagram, Appendix 11). After 26 duplicates were removed, 1,774 citations were screened against title and abstract. From this set, 1,622 citations were excluded as being irrelevant and 152 studies were read in full to assess eligibility. Of this set, 147 studies were excluded as being either wrong outcomes or wrong research design (i.e., quantitative research in design) (Appendix 12). Five papers covering four studies were included as the final set (Appendix13). The papers by Sjursen et al., (2014, 2015)[95,96] are companion papers.

Descriptive analysis

The publication dates ranged from 2004 to 2016. Based on the country of the lead author, two studies originated in Sweden (Marell et al.[97], Stahlnacke[98]), two papers (one study) in Norway (Sjursen et all, 2014;[95] 2015[96]), and one study in New Zealand (Jones, 2004[99]). The total number of participants was 71. Of this total set, there were 27 women and nine men, while the same seven women and five men were included in both studies by Sjursen et all.[95,96] One study (Jones, 2001[99]) included 35 participants but did not specify the participants' sex. Two studies reported the participants' age ranges (Marell et all.[97] and Sjursen et al.[95,96]) and combined those ages ranged from 37- to 65-years-old. All participants were in the role of patients, representing themselves. No one was in the parental role representing the experience of children. Qualitative research methodologies included one grounded theory (Marell et al.[97]). The other studies did not specify a specific qualitative methodology. Data collection methods included semi-structured interviews, and one study conducted seven focus groups (Jones[99]). Data analysis included thematic analyses (Sjursen et al.[95], 2015[100] and Jones[99]), one study used content analysis (Stahlnacke[98]), and the grounded theory study (Marell et al.[97]) used a constant comparative method to establish codes, categories, properties, and dimensions. See Characteristics of Included Studies table in Appendix 14.

It is important to note that the four included studies represent a focus on patients' experiences with amalgam, and specifically health complaints and symptoms that people attribute to dental amalgam. No studies were located that addressed patients' experiences with composite resins. Furthermore, the research questions of the included studies focus on patients' negative experiences and health complaints with amalgam, only. Patients' participation in these studies was based on their willingness to discuss their health-related

symptoms, complaints, and other problems they perceived or attributed as related to dental restorative materials.

Critical appraisal of individual studies

Overall, the quality of the studies was high (Appendix 15). All four studies obtained a “no” for the first question, which addresses the congruency between philosophical perspective and research methodology because no philosophical perspective was clearly reported by the authors of any of the included studies. All studies, however, included a su fficient description of their study objectives and methods to allow for an assessment of the methodological congruence between research questions and research methods (Q2), data collection (Q3), data analysis (Q4), and interpretation of results (Q5). In all cases, studies were assessed as methodologically congruent, supporting the credibility of the data and analysis. Additional questions that were answered “yes” for all studies include the question about obtaining ethical approval (question 9) and the question about whether the conclusions drawn from the research flow from the analysis and interpretation of the data (question 10). Question 8 reflects the adequate representation of the participants’ voices and one study (Jones et al.[99]) obtained an “unclear” in this appraisal, while the remaining studies provided sufficient detail to warrant an assessment describing the adequate representation of participants, and their voices. The study report by Jones et al.[99] failed to provide a statement of researcher positioning culturally or theoretically (Q6), and researcher reflexivity (Q7), indicating that the influence of the researcher on the analysis and interpretation of data may not have been adequately accounted for and that may call into question the credibility and confirmability of the analysis. Given the similarity in results across included studies, however, this does not appear to be a concern in this instance and may be an issue of poor study reporting as opposed to poor study conduct.

Although a small number of studies were identified to inform the policy question, these studies were assessed to be of high methodological quality and thus are able to provide strong evidence of the patients’ experiences as they relate to amalgam restorations and the particular experience of health complaints perceived to be attributable to amalgam restorations. No studies were located that investigated patients’ experiences with composite resins, which suggests that the body of evidence identified as eligible for this review does not provide a complete view of patient perspectives as they relate to the policy question.

Meta-synthesis

Twenty-three findings were extracted from the included studies. These findings were aggregated into five categories, which in turn were aggregated into three synthesized findings. The relationship between findings, categories, and synthesized findings is depicted in Appendix 16 and Appendix 17.

The process of aggregation is a pooling together of common concepts across all the studies, bearing in mind that those statements that reflect different or contrary opinions must also be represented. All participants were adults and two of the studies provided an age range of between 37- and 65-years-old. The participants were for the most part in the prime of their working careers and the situations they described reflected their need to juggle their working and family lives, all the while struggling with a variety of symptoms some described as debilitating and others described as wearying — all that they attributed to dental amalgam restorations. There is no single set of symptoms that all participants describe, and no clarity as to the primary cause of these symptoms, which participants perceived to be the result of amalgam restorations. Some participants report allergic reactions such as burning

and lesions in the mouth, whereas others have more systemic ailments such as pain and fatigue. It is important to note that these four studies focused only on health complaints and symptoms that participants attribute to amalgam restorations and that no qualitative studies were identified that investigated positive experiences with amalgam or either positive or negative experiences with composite resins. In this case, these studies cannot support a causal relationship between amalgam and negative health complaints, and the lack of literature does not mean a lack of positive experiences.

Synthesized finding 1: Something is not working — trying to understand health complaints

This synthesized finding highlights the participants' need to comprehend and make sense of a myriad of different symptoms they were experiencing, which ultimately they attributed to be as a result of their amalgam restorations. It was generated by three categories and a total of 16 findings.

Category 1: Range of ill health experiences — oral, somatic, mental, long term

The following studies contributed to this category: Sjursen et al.[96] 2015; Stahlnacke et al.;[98] Jones et al.;[99] and Sjursen[95] 2014.

Before linking their experiences to dental amalgam, participants reported multiple symptoms and described feeling puzzled and overwhelmed by their complaints. Some participants more immediately perceived their complaints to be associated with their amalgam restorations, whereas, for others, this association was not immediately apparent. The confusion expressed by many participants was due to their initial lack of understanding of the source of their complaints. Across the four studies, it was clear that there were a range of symptoms being reported, with some symptoms such as pain being common throughout. Many participants reported issues directly related to the mouth. For example, one participant mentioned, "you feel sore and have so many, many blisters in the mouth, I had, you know" (Stahlnacke[98]). Others described a combination of symptoms such as pain, and more general or vague symptoms. This participant's quote not only illustrates the range of experiences but also the struggle to understand the reason for the poor health:

> I was in so much pain, and I also felt, for a while, that I had such a poor memory (sighs). I cannot say if that was because of stress caused by having to fight the pain, but I did feel 'out of it' in a way. I really did (Sjursen et al. (p4)[96] 2015)

It was common for participants to report a decrease in their social lives as a result of their symptoms, some feeling too bad to engage in interactions while others did not feel as if they had the strength. Consequently, loneliness and depression were common experiences, too.

In her study, Jones[99] concludes that the psychological problems described by participants were twofold:

- problems that may be attributed to mercury toxicity such as memory loss, mood swings, and loss of sensation
- problems related to the consequences of having symptoms that were not readily diagnosed, namely self-efficacy, the social stigma of being labelled a hypochondriac, the concomitant loss of social support, and the stigma of being referred for psychological or psychiatric assessment (Jones et al.[99]). "Participants in some focus groups spoke about suicidal thoughts, including praying to die and dreaming of death." (Jones et al.[99]).

Category 2 — Identifying the source of the symptoms

Three studies contributed to this category: Sjursen et al.,[95] Marell et al.,[97] and Sjursen et al.[96]

Participants described that, following amalgam restorations, they had a feeling that their entire bodily and psychological functioning was influenced from the outside, which they described as a feeling of being poisoned. They searched for causes and reasons that might explain their experiences. Often, participants related their constellation of symptoms to other illnesses they had experienced before. Given the somewhat vague nature of these symptom constellations, they were often compared to the experience of being ill with influenza. For example, one participant described symptoms as being like an experience of the flu and established a connection of these symptoms with their teeth — although we are not privy to the rationale that has made this connection:

> That it might have some connection with my teeth that I was often so terribly tired, had pains in my body and felt dizzy and nauseous, had problems roughly like what you think of if you get the flu. (Stahlnacke et al. (p125)[98])

In their attempt to understand their conditions, participants did their own research, talking with others who might help or guide them to some answers. Driven by the sense of "being poisoned," many participants hunted for information about poisoning, and mercury poisoning in particular. They typically reported identifying resonance with the symptom picture of mercury poisoning, which they felt provided some clarity to their experiences. One such participant described this process:

> And when I was at the specialty unit, I contacted the organization for amalgam poisoning and I read everything I could get my hands on. And then I felt that I had all the complaints (laughs). (Sjursen et al. (p223)[95] 2014)

Category 3 — Input from trusted others as guidance

The studies by Sjursen et al.[95] and Stahlnacke et al.[98] contributed to this category.

In their attempt to identify the cause of their symptoms, participants often turned to others for guidance. Some participants received input and guidance from trusted others who directed them toward what they felt could be the cause of their symptoms. This made the guidance easier to accept. One participant reported that he was guided by his wife, who was a dental assistant; another participant received guidance from the dentist:

> Well, it was the dentist who first put me on to the idea, you know...He saw how bad my teeth were and how much pain I was in... I described how I felt at the time, how painful it was, and how it burned and ached, you know. (Sjursen et al. 2014 (p222)[95])

In some cases, the trusted other also provided direction in how to address the problem. In this instance, the participant's dentist instructed the participant to remove the amalgam, indicating that he or she would not feel better until that was done:

> "I had all the amalgam removed and my dentist said, 'you have to get rid of it; you won't get better before that,' he said." (Stahlnacke et al.[98])

The move to treatment of the amalgam-related illness is addressed in this next synthesized finding.

Synthesized finding 2: Struggle to obtain redress — searching for help, treatment and a reliable diagnosis.

This synthesized finding describes the interactions with the health care system and was generated by one category and a total of three findings.

Category 4 — Encounters with health care professionals

Four studies contributed to this category: Marell et al.;[97] Stahlnacke et al.;[98] Sjursen et al[96]; and Jones.[99]

Many participants were uncertain about the cause of their complaints and sought out health care professionals, including family physicians and dentists, to help diagnose, explain, and treat their ailments; the encounters were sometimes good, but more often than not frustrating. One participant was well-supported by the healthcare professional and was therefore pleased by the encounter: "I got affirmation, she told me a lot about the disease, she told me exactly how to act and, and what, what was important to do." (Stahlnacke et al.[98])

However, many other participants struggled with their physicians or dentists, who they perceived to be dismissive when no clear diagnosis was evident. One such participant clearly illustrates her devastation at being dismissed:

> I remember I was crying when I walked away from the doctor. I figured there was something wrong with me, but nothing was shown, all the investigations and tests showed nothing. They said that I'm healthy even though I feel like this! (Marell et al. (p4)[97])

Jones reported that her participants

> had 'every test in the book' from blood counts to scans. As the tests never showed anything abnormal, many had been told by doctors that they were 'making it up'… As illness persisted without a medical label or as a psychosomatic condition, these people experienced the negative social stigma of being labelled 'a hypochondriac'. (Jones (p146)[99])

Participants who engaged with health care professionals who practised alternative health care (not further specified) were generally pleased with the support and care they received from these professionals.

It is important to reiterate that the included studies focused on participants' negative experiences related to amalgam restorations, with many of their complaints being general and vague in nature and hence likely difficult to diagnose. Consequently, it is understandable that their interactions with health care professionals may not have been viewed as consistently positive.

Synthesized finding 3: Amalgam removal and the journey toward health.

This synthesized finding portrays the journey, the change of restorative material, and the path forward toward health. It was generated by one category and a total of six findings.

Category 5 — De-amalgamation and detox

Three studies contributed to this category: Jones,[99] Stahlnacke et al.,[98] and Sjursen etal.[96]

Participants chose one of several options once they identified what they considered to be the cause of their illness. Some elected to remove all amalgam restorations and replace them with composite resin restorations; others elected to become edentulous (not having

teeth). Still others did not remove any of their amalgam restorations, with the cost associated with the procedure being identified as a barrier.

Besides cost, for those participants who reported negative experiences associated with amalgam restorations, the process of removing amalgam was also fraught with difficulty. For some participants, having the amalgam fillings replaced and the time immediately afterwards was often a period of intense adverse reaction. It is important to note that these adverse reactions were assumed by participants to be associated with the removal of the amalgam restorations, although no supporting external evidence to confirm the assumption was reported. One participant clearly described an adverse reaction during that period:

> Sometimes when I had amalgam fillings replaced, I felt absolutely terrible afterwards. Sometimes I even had to stay home from work…I was in pain, I was frightfully tired, and I felt nauseated. (Short pause) It was obnoxious. (Sjursen et al. (p221)[95])

Jones reported that after de-amalgamation and detoxification, the participants in her study were:

> surprised both at the return of lost sensation and the speed of recovery. They had not anticipated any immediate benefits but reported the lifting of the 'brain fog,' improved smell and taste, an absence of colds and flu symptoms, and the end of the metallic taste. This was equated with a major health gain. (Jones (p146)[99]).

However, for some participants this return to feeling healthy took a little longer. One participant explains the length of time before feeling better: "I can still feel a little now, but I've become much better; but it probably took, once all the amalgam was away, it took about two years." (Stahlnacke et al.[98])

With a constellation of symptoms that tend to be vague, some participants were uncertain of the role of amalgam removal in their change of health status. One participant explained that they would need to have psychic powers to know for sure:

> This amalgam removal, I do believe it has had an effect, together with all the other things. But I would have to have psychic abilities to know exactly how. As I have told you, there are still periods in which I feel quite poorly and beside myself, but I do feel much better now. I really do. (Sjursen et al. (p6)[96] 2015)

Participants also mentioned that removal of their amalgam restorations was like "a worry crossed off the list" in that they would not have to be concerned about it with regard to their future health (Sjursen et al[96] 2015).

What was clear to most participants was the perceived need to follow the amalgam removal process with a structured detoxification program. Jones commented that in her study and the seven focus groups she conducted to discuss this process with her participants:

> every group had some participants who mentioned a 'bath' metaphor as a heuristic that explained deamalgamation and detox. Their body was likened to a bath, and dental amalgams likened to a dripping tap. For a person with dental amalgams, the tap was turned on, but with amalgam removal the tap was turned off. In the metaphor, this left 'water in the bath' and it needed to be drained. To detox was to 'pull the plug'. (Jones (p144)[99])

Summary of Results

Whereas the research question was formulated to engage a qualitative research synthesis to understand the patients' experiences around both amalgam and composite restorations, four studies that focus on health complaints attributable to dental amalgams were located. No studies were identified that focused on experiences with composite restorations, nor experiences with amalgams other than health complaints. The results therefore describe a narrow set of experiences, and are not generalizable to the broader set of experiences with either restoration material. It is possible that descriptions of the patients' perspectives with amalgam, as well as composite resin restorations, lie in the quantitative research evidence. Hence, this qualitative synthesis cannot address the entire research question on patients' perspectives and experiences. However, through the integration of the participants' voices, it does provide insight and understanding into the experience of those patients who feel they have been afflicted due to their amalgam restorations, and their struggles to address and resolve this experience.

Through a focus on patients with amalgam restorations and their experiences of perceived adverse reactions to the amalgam, this review highlights their struggle to be understood and believed as they search for a cause for their sense of ill health. Once determined to resonate with the symptoms of Hg poisoning, some patients identified the option to follow the path of de-amalgamation and detoxification. Even though the path of removing amalgam, for some, was described as difficult, and one that may not provide immediate health gain, this path did appear to provide relief from worry of a potential toxic influence on health at a later stage.

Implementation Issues

This section addressed the following research questions:

Research Question 5: What is the current use of amalgam restorations in Canadian dental practices or programs?

Research Question 6: What is the current use of composite resin restorations in Canadian dental practices or programs?

Research Question 7: What factors influence the use of amalgam or composite resin restorations in Canadian dental practices or programs?

Research questions 5 to 7 aimed to gather information on relevant implementation considerations for using dental amalgams and composite resin fillings in Canada. Implementation considerations may include policies, funding, dental care practices, and considerations relevant to dental providers and patients including considerations for special groups of patients, such as those in rural or remote settings or of low socioeconomic status.

Methods

To understand the current context and implementation issues or considerations associated with the use of dental amalgams and composite resin fillings in Canadian dental care settings, telephone consultations and a review of the published literature were conducted. A survey of stakeholders was not performed, as information from the literature and consultations were expected to be sufficient.

Data Collection

Stage 1: Interviews

Interviews were conducted with targeted experts and stakeholders identified through the clinician networks managed by CADTH to provide a general overview of policy, funding, practice, and issues related to using dental amalgams and composite resins in dental care settings in Canada.

To guide the interviews, a semi-structured interview guide was used (Appendix 18). Interview questions related to implementation were developed based on the research questions and the type of expert being consulted. Interviews were conducted by phone by a CADTH staff member, and follow-up questions or clarifications were conducted by email. Notes were taken during the interviews and copies of email correspondence were retained for the purpose of subsequent analysis. Written consent to publish comments and names, where required, was obtained.

Stage 2: Literature Search

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print, In-Process records and daily updates via Ovid, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts

were dental amalgams and composite resins. The search strategy for the dental amalgam and composite resin concepts were based on the Q2 search strategy.

A methodological filter was applied to limit retrieval to studies relevant to implementation issues. Additionally, the search was limited to articles related to the Canadian context. Retrieval was not limited by publication year or language. The search strategy is available upon request.

The search was completed on June 29, 2017. Monthly alerts were established to update the searches until February 1, 2018. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback period of the final report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economics-related resources, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Eligibility Criteria

We included English- and French-language reports that described implementation and context issues, including barriers and facilitators, associated with the use of dental amalgams and composite resins in dental care settings in Canada. Literature was limited to Canadian-only studies, or studies discussing the Canadian context, published after 2000. This decision was made because the Canadian context for the use of dental amalgam and resin composites was primarily of interest for this HTA, and recent literature was reviewed to more accurately reflect the current landscape and available materials of dentistry. The choice of restricting by year differs from the original protocol, and was an ad hoc decision by the researchers, based on the lack of relevance of older articles to current dental practice context. The year 2000 was chosen, as this was the year that Environment Canada started conducting studies on mercury-based wastes from dental offices. One year after that, in 2001, an endorsement of a Canada-wide standard on mercury for dental amalgam waste took place.[101]

Screening and Selection of Articles for Inclusion

Articles were screened and selected for inclusion based on the eligibility criteria by one reviewer. First, titles and abstracts were reviewed to identify potentially relevant papers. At this level of screening, only one reviewer needed to include the article for it to move to full-text screening.

Then, one reviewer screened the full text of all potentially relevant reports retrieved for a definitive determination of eligibility, and ineligible reports were excluded from data extraction.

Data Extraction

Data extraction was performed by one reviewer. The data were extracted to a Microsoft Word table and included bibliographic details of included papers, reported implementation barriers and facilitators, and other key findings related to implementation and relevant context information.

Data Analysis Methods

A narrative summary of the findings was written by one reviewer. Wherever possible, the findings were categorized based on the INTEGRATE-HTA framework.[102] A description of varying factors that both facilitate and impede the use of both amalgam restorations and resin composite restorations is presented.

Results

Five stakeholders in dental care in Canada were consulted for their feedback on the extent of the use of dental amalgams and composite resins, as well as the context of use and implementation issues related to these materials. These stakeholders represented the following areas in dentistry: academia and research, hospital dentistry, private practice, the Canadian Dental Association, and a publicly funded dental program in Nunavut.

The implementation literature search yielded 220 citations. Out of these, nine English-language reports that described implementation and context issues, including barriers and facilitators, associated with the use of dental amalgams and composite resins in dental care settings in Canada were eligible for inclusion. All included studies were Canadian literature or had relevant information pertaining to the Canadian context.[103-111] Included studies provided information on the teaching of restorations in dental schools,[104,106-108,111] patient-specific care, patient concerns or patient or provider preferences,[105,106,108-110] minimally invasive dentistry,[106,111] contraindications for materials,[103,110] and the cost of materials or funding.[108,109] Five of the nine relevant studies were published prior to 2012.[104,106-108,110]

Relevant information from the literature and the stakeholder consultations as it relates to each of the INTEGRATE-HTA context and implementation domains is subsequently described. The findings best fit within the following INTEGRATE-HTA framework's implementation and context domains of "policy," "funding/cost," "organization and structure," "provider," and "sociocultural."

No data were identified regarding the current use of amalgam and composite resin in Canada (research questions 5 and 6). Findings from the literature search and interviews are focused on considerations regarding the use of these restorative materials (research question 7).

Policy

The consultations with stakeholders identified that, in Canada, there is no specific policy in place to dictate the use of one material over another in dental practices. According to the Canadian Dental Association, the current status of practice in Canada is that "dentists should use the most appropriate material for the patient, in consultation with the patient" (Dr. Benoit Soucy, Canadian Dental Association, Ottawa, ON: personal communication, 2017 Sep 7).

However, a "changing dynamic" in the use of these materials, which is mainly driven by a "significant environmental context," was reported (C.Q.: expert opinion, 2017 Aug). Canada signed the Minamata Convention agreement in 2013; however, the agreement does not exclude the use of dental amalgams in dental practices. To address the environmental issues related to the toxicity of mercury from dental amalgam waste, the Canadian Dental Association established a Memorandum of Understanding with Environment Canada in 2002.[112] This Memorandum of Understanding established the use of best management

practices for dental amalgam waste, for all dental practices in Canada. According to this agreement, all dental practices across the country that generate amalgam waste are mandated to purchase amalgam separators to address the release of mercury. With a coordinated educational effort by the Canadian Dental Association and Environment Canada on pollution prevention plans for dental offices, it is estimated that, as of 2012, approximately 97% of dental offices in Canada follow best management practices for amalgam disposal.[12]

In Canada, most dentists (approximately 90% to 95%) are in private practice (Dr. Benoit Soucy: personal communication, 2017 Sep). However, public dental programs are available for different groups of patients who do not have access to dental coverage benefits.[81] In Nunavut, for example, most dental care is provided through public dental health programs and all Inuit patients (approximately 90% of the population) are covered by the Non-Insured Health Benefits (NIHB) Program provided by Health Canada. This program does not dictate the use of any particular material; the choice of materials rests with the dental provider (Dr. Ronald Kelly, Department of Health, Government of Nunavut, Iqaluit, NU: personal communication, 2017 Sep 20).

However, it has been reported that, in Quebec, patients less than10 years of age who are covered by the government-funded provincial dental plan are less likely to have a posterior restoration with a composite resin, as the provincial dental plan covers only the cost for amalgam restorations in the posterior teeth. Exceptions are maxillary premolars on mesial and buccal surfaces for which composite resin is covered.[108]

Cost Considerations

Several aspects of cost considerations as they relate to the use of these materials were discussed with stakeholders and were also reported in the literature (limited reporting).[108,109] The majority of dental practices in Canada are private. In addition to material suitability, durability, and safety, factors that may be of importance to private practitioners in Canada are cost considerations, margins of profit, and efficiency of practice, and these factors may contribute to dentists' decision-making regarding the choice of material. Provincial fee guides are available in Canada, although those only provide suggestions for fees for restoration procedures.[81]

When it comes to choosing a material over another, dentists may charge a higher fee for using composite resin over amalgam. Stakeholders in our consultations discussed that fees charged by dental practices often correspond to:

- direct costs (i.e., composite resin is more expensive to purchase compared to amalgam
- indirect costs (i.e., composite manipulation is "technique-sensitive," takes longer to apply, and requires more adjunct devices compared to an amalgam restoration)
- the failure rate of the restoration (i.e., in many cases, the restoration with a composite material will fail more often than amalgam and therefore will have to be restored more frequently).

So, while in some provinces (e.g., Ontario) the suggested fee guides for composite and amalgam restorations do not differ by much, it is possible that a dental practice using mostly composite materials will have more revenue due to an increased frequency of restorations (Dr. Susan Sutherland, Sunnybrook Health Sciences Centre, Canadian Association of Hospital Dentists,Toronto, ON: personal communication, 2017 Aug 24).

During consultations, it was mentioned that because amalgam separators are considered mandatory for use in many if not all jurisdictions, all dental clinics should be equipped with these devices. In Nunavut, not all clinics have amalgam separators, and composite resins may be utilized in preference to amalgam for this reason (Dr. Ronald Kelly: personal communication, 2017 Sep).

In Nunavut, contractors are responsible for buying the consumable materials to be used in dental clinics "and may buy these materials in bulk (at a better price)" (Dr. Ronald Kelly: personal communication, 2017 Sep). As shipping materials between communities in the North is difficult, purchasing and shipping only one type of restoration material may also contribute to the efficiency of the shipping process and help keep the costs down (Dr. Ronald Kelly: personal communication, 2017 Sep).

In our consultations, it was mentioned that, overall, with composite restorations, there may be a financial incentive for dental practices, as they may yield a larger margin of profit when they perform this procedure.

Because of the changing properties of composites, reimbursement policies for public dental programs are changing, as well. It is reported that some public programs may reimburse different restorations for anterior and posterior teeth, such as the Quebec Health Insurance provincial dental plan for children less than 10, which reimburses amalgam restorations in posterior teeth on mesial and buccal surfaces (for which composite is covered), except for restorations for maxillary premolars; and for aesthetic restorations in anterior teeth.[113]

An overview of reimbursement policies for public dental programs in Canada can be found in the CADTH Environmental Scan on public dental programs and reimbursement for dental restorative procedures.[81]

Dental Practice

According to Lynch et al.,[106,111] the dental field as a whole has moved to more "minimally invasive" dentistry practices. Using composites obviates the need to remove sound tooth tissue for retention (i.e., resin composite requires less tooth removal than amalgams), which reduces the subsequent risk of tooth fracture and reinforces the remaining tooth substance.[106,107,109,111]

During our consultations, it was acknowledged that, in some dental practices, the option of amalgam is not offered to patients (only offer restorations with composite resin). Possible reasons behind this and other dental practice-related issues that may affect the use of these materials included health-related concerns regarding mercury in amalgams, dental practice efficiency cost, and profit.

In terms of mercury-related health concerns, dental providers in our consultations reported that this is not a concern for dentists and their patients. However, it was recognized that some dental practices advertise themselves as "green" or "holistic" dental practices, not offering amalgam as an option; or they encourage collaborating with physicians for "detoxification" from amalgam fillings.[105] These practices, which are not supported by scientific evidence, are not supported by the Canadian Dental Association (Dr. Benoit Soucy: personal communication, 2017 Sep).

As reported in our consultations, for dental practices, efficiency matters and when there is only one material, one type of equipment and one technique that the dentist (and dental

practice staff such as dental hygienists) has to focus on efficiency improves. In addition, it was also discussed that using only one material keeps the cost under control as well and leads to a good return of investment. However, even for those practices that focus on one material (i.e., composite) are required to have amalgam separators because they still generate amalgam waste when they perform removals of amalgam restorations (Dr. Benoit Soucy: personal communication, 2017 Sep).

Regarding potential health concerns for dental staff, dentists in our consultations reported that they believe these are being addressed sufficiently, as there are modern and safe methods of handling and disposing excess mercury and therefore the exposure to mercury for dental practitioners is likely minimal.

Dental Provider

Attitude toward materials and knowledge of underlying pathology

The properties, clinical indications, and contraindications of amalgams and composite resins are important parameters to consider prior to using these materials in dental practice.[109,110]

Dentists in our consultations indicated that amalgam is used in cases where other materials are not indicated (i.e., higher risk for restoration failure) and aesthetic considerations are not a concern. In general, it was reported that amalgams perform better in oral environments with high susceptibility to caries, where there are difficulties with moisture control, and when a big restoration is needed (amalgam restorations last longer). On the other hand, for a patient with low caries susceptibility, composites may perform better. For better performance and maintenance, composite materials also need a “dry tooth bed” (i.e., no saliva, no blood). If this is not the case, it was discussed that amalgam is a more suitable and “predictable” material (Dr. Benoit Soucy: personal communication, 2017 Sep).

Patient profile is an important consideration for restoration material choice. For example, for patients with special needs or geriatric patients for whom oral hygiene cannot be reinforced, amalgams are a more suitable option, as the presence of constant plaque in such an oral environment damages the adhesive bonds (i.e., chemical bonds formed by composite). (S.E.: expert opinion, 2017 Sep). One stakeholder working mainly with patients older than 50 years, with multiple comorbidities, reported that she changed her practice with posterior teeth from using primarily composites to using more amalgams; she found that she encountered an increased rate of recurrent decay in this population and a need for frequent replacements. In this stakeholder’s experience, composites do not last as long, are more expensive, and also cause sensitivities (Dr. Susan Sutherland: personal communication, 2017 Aug).

However, it is reported that, over the past few years, improvements in bonding agents have increased the “predictability” of resin materials, and this improvement in the material is one contributor to its increased use.[107-110] Stakeholders also discussed that, by using the appropriate light-curing device, newer composites can be placed more quickly than amalgams.

Education and training

Stakeholders discussed the sociocultural and educational shift that has taken place regarding using amalgams and composite resins in dentistry.

During the consultations, it was discussed that, despite the fact that dentists are trained to provide the most appropriate treatment for patients, strong patient preference for “white

teeth" (i.e., aesthetic-oriented society), combined with an inherent professional ethos in dentistry for cosmetic care, may contribute to the increased use of composites in dental practices.

Stakeholders reported that, to their knowledge, dental schools teach dental restorations with both materials (with the emphasis of teaching equal for both materials), and that dentists are trained in both the benefits and disadvantages of amalgams and composite resins.[108] However, it was also reported that, depending on school philosophy, one material may be favoured over another. According to Lynch et al.,[107] in 2006, the teaching of amalgam and resin composites in Canadian dental schools was reported to be approximately equal (i.e., 50/50). By 2012, an increase in teaching composite resin-filling techniques was reported and both US and Canadian dental students were gaining more experience in placing posterior resin-based fillings.[111] It was also mentioned that, in Canadian dental schools, there was increased pressure to use and teach posterior resin composite restorations as a result of the discussions by Health Canada regarding the amalgam issue.[108]

Where dental practitioners train and the type of continuing education they receive is important. For example, during their training, new dentists are often exposed to clinicians who teach them what they do (i.e., most use composites). Depending on the level of expertise and comfort, dentists will be teaching more of what they are comfortable with. If dentists are not taught or trained well on using one material, they will gravitate toward using the material they are more familiar with (C.Q.: expert opinion, 2017 Aug; S.E.: expert opinion, 2017 Sep).

In our consultations, it was also reported that an age and cohort effect may be a consideration when choosing one material over another. For example, newer dentists may want to try new products ("to be modern, sophisticated providers") and adhere to what are perceived as "non-toxic" materials, thus also satisfying patients' preference (C.Q.: expert opinion, 2017 Aug). More experienced dentists or dentists of an older generation would perhaps advocate for more frequent use of amalgam (S.E.: expert opinion, 2017 Sep). Continuing education on restoration materials was also reported as important to dental practice given that composite materials continue to evolve (i.e., new versions of composites are developed) at a fast pace.

Patient preference and dental practice

In addition to clinical expertise (skills and competencies of dentists) and level of evidence on each of these materials, patient preference contributes significantly to a dentist's decision to use one material over another. According to one stakeholder, "dental care is a private industry, where the patient is the buyer and, as such, they have a very strong decision-making power. As a patient/customer, you are buying a health product" (S.E.: expert opinion, 2017 Sep). It was discussed that, although it wasn't identified in the literature regarding patient preferences (see Patients' Perspectives and Experiences section), dentists need to be cognizant of the drive regarding white fillings. Part of a dentist's job is to educate patients about their options and allow patients to ask questions about them so that there is a clear understanding around what each technology can provide. However, during the consultations, it was also mentioned that, often, dentists oblige with patient preference for one material while on the other hand dentist preference for composite is stronger, and often the choice is not even presented to the patient.

Patient Considerations

Socio-cultural considerations

Although not identified in the qualitative literature (see Patients' Perspectives and Experiences section), patient preference for "white fillings" was described as a significant factor influencing the increased use of composite resins over amalgam in dental practices. Stakeholders and literature findings report that patient preferences for composites over amalgams is mainly driven by aesthetic and health concerns.[106-110] Other considerations reported in our consultations include concerns for toxicity and safety (i.e., patients think that composites are safer than amalgams), as well as cost (when dental care fees are not covered by insurance).

As reported during the consultations, the socio-cultural trend for "straight, white teeth" combined with a perception of health hazards associated with amalgams often drives a strong patient preference for white fillings. In many cases, patients "demand" composites, even in posterior teeth, without really having a solid understanding of the treatment options or the potential risks of composites (Dr. Benoit Soucy: personal communication; 2017 Sep). Many patients also request changing all of their amalgam restorations with composite resins "despite the fact that the amount of mercury in the fillings is low" (S.E.: expert opinion, 2017 Sep). This shift in patient culture has taken place approximately throughout the last 20 to 25 years, when the public became aware (through patient advocacy groups and the media) that dental amalgams contain mercury and started being concerned for having amalgams in their mouths. Although not identified in the qualitative literature, the experts consulted also noted that environmental concerns are also present among patients.

Patient Cost Considerations

In addition, as dental care for most Canadians is not covered by public plans, patients are responsible for paying for their treatment. Therefore, the aspect of financial considerations or reimbursement options is important in their treatment preference.

In Nunavut, even though many people present cases for which dental amalgam would have been the preferred material to use (because of risk factors, oral health, etc.), composite is still the most frequently used direct restorative material (estimated at approximately 80% to 90% of restorations) (Dr. Ronald Kelly: personal communication; 2017 Sep).

On the other hand, it was reported that, when patients are offered information regarding the benefits and the clinical appropriateness of using amalgams, aesthetic concerns usually do not overrule health concerns and potential benefits (Dr. Susan Sutherland: personal communication; 2017 Aug). A survey of Canadian dental schools revealed that many course directors state that they provide guidelines on the choice of restoration material for varying clinical cases, but that patients ultimately make the material choice in their faculty clinics.[108] Patients need to understand the risks associated with having more restorations or the adverse effects associated with using composites, as well.

Summary of Results

There are factors that influence the use of one type of restorative material over another.

Across Canadian jurisdictions, there are no specific policies that dictate the use of dental amalgam or the use of resin composites.

Geographical location (e.g., Canada's North or remote communities) can be a factor and often limits available materials. Shipping multiple materials to remote northern communities is costly and inefficient, so often providers only ship resin composites, thus limiting the use of amalgams in these areas.

The majority of dentists in Canada are in private practice. Factors such as profit margin and efficiency of practice are therefore additional considerations for many Canadian dentists and can affect the decision-making process for restorations.

The dentistry field often practices "minimally invasive" dentistry, which makes composite resin an attractive option, as it obviates the need to remove a lot of sound tooth tissue when compared to amalgams. Dentistry education in universities does not appear to focus on one restoration over another, but dentists may choose to use materials they are more comfortable with, that are newer and "more sophisticated," or that their supervising dentist primarily used.

Patient profile and clinical indications are of importance to dentists when deciding on which restoration to use, as amalgam and resin composites have different mechanical properties. These properties can make some patients contraindicated for certain materials. There is large socio-cultural and patient pressure to provide restorations that maintain a "straight, white" appearance of teeth for the patient. As the patient is the customer and has a strong decision-making power regarding their care, this can affect the decision for a provider to use resin composites over amalgams.

Conclusion

There are many factors that influence the use of one type of restorative material over another. These include funding and reimbursement, the dental provider's setting (public or private), provider attitudes and perceptions, provider education and training, patient perceptions, education and preferences, and sociocultural attitudes toward dental restoration materials. It is expected that dental providers educate patients about the most appropriate choice of restoration for their clinical case, but patients may make choices based on a variety of reasons, such as what materials are reimbursed and are available in their area, aesthetic concerns, health concerns, and what is recommended by their dentists. Ultimately, each individual case and patient are different, which means these factors can both act as barriers or facilitators in the use of different restoration materials in Canada.

Knowledge Mobilization

The implementation issues identified will guide the development of knowledge mobilization activities, tools, and tactics to support the implementation of any resulting decisions or changes to the health care system or to health service delivery.

Environmental Impact

This section addressed research question 8: What are the environmental effects associated with the use of dental amalgams versus composite resin restorations?

The dental profession relies upon a variety of materials and processes to achieve its goals, although these are not without some risk to the environment. Here, we focus on environmental risks associated with the two main restorative materials used in dentistry — amalgam and composite resins.

A comparative assessment of potential environmental effects associated with the use of dental amalgams versus composite resins took guidance from the *Canadian Environmental Assessment Act, 2012*[114] and the US Environmental Protection Agency's Ecological Risk Assessment framework.[115]

Methods

Literature Search

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with Epub ahead of print, In-Process records and daily updates, via Ovid; Embase (1974–) via Ovid; and Scopus and TOXNET. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Most subject headings were focused and most keywords were limited to title, only. The main search concepts were dental amalgams and composite resins. The search strategy for the dental amalgam and composite resin concepts were based on the Q2 search strategy.

Methodological filters were applied to limit retrieval to studies related to environmental assessment. Retrieval was not limited by publication year but was limited to the English or French language. Conference abstracts were excluded from the search results. The search strategy is available upon request.

The search was completed on June 16, 2017. Monthly alerts were established to update the searches until February 1, 2018. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback period of the final report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

Selection criteria

One reviewer screened the titles and abstracts of all citations retrieved from the literature search. For citations that appeared eligible for inclusion (an a priori listing of keywords that guided our search are provided in the project protocol[29]), the full text of these articles were

retrieved and assessed (by the same reviewer) to determine eligibility. We focused our search on papers published since 2006 to cover the most relevant period (i.e., declining use of dental amalgam coupled with the emergence of the use of composite resins), and those based in relevant comparison countries (Canada, the US, Australia, New Zealand, the UK, and members of the European Economic Area). The clinical use, material composition, and/or environmental impact of amalgam and resins have changed throughout preceding decades, and thus we limited our search to recent years to focus on the most pertinent literature.

Articles that provided insight into the potential environmental impact associated with dental amalgam and composite resin restorations were included. For example, the impact may relate to mercury exposure from dental amalgams and BPA present in composite resins. However, to enable a comparative assessment, we did not restrict our search to papers that examined both amalgams and resins but, rather, explored each topic independently.

Based on our initial findings and review of the literature, further searches to identify additional information on the environmental impact of dental amalgams and composite resin restorations were conducted by reviewing key papers cited in the documents retrieved.

Data Extraction and Content Analysis

From each relevant article, the bibliographic details (authors, year of publication) and issues related to the environmental impact identified were captured by one reviewer. For both amalgam and composite resin, we then categorized the findings into key risk assessment criteria, namely hazard identification (e.g., what potentially toxic chemicals are present in the material), exposure assessment (e.g., how might key receptors be exposed), and toxicology (e.g., what the potential toxic effects might be). The findings were summarized narratively and, when possible, quantitative estimates were derived to try to best reflect the current situation in Canada.

Results

Quantity of Research Available

The literature search identified 1,684 unique citations and 12 articles were identified from other sources. One reviewer reviewed 56 full-text articles, and 19 were included in this review. It is noted that no single study performed a detailed comparison of amalgam and composite resins in terms of environmental impact, and that most papers on the topic focused on key chemicals within these materials rather than on the material itself.

Content Analysis

Dental Amalgam

Dental Amalgam — Hazard Identification

Dental amalgam is formed from the amalgamation of powdered silver, tin, and copper (among other elements) with mercury. Environmental risks have exclusively focused on mercury, and thus is the focus here. Mercury is a naturally occurring element that exists in three chemical forms: elemental or metallic mercury (Hg^0); inorganic mercury compounds (Hg^{2+}, Hg^{1+}); or organic mercury compounds, with the main form being methylmercury (MeHg).[116] Dental amalgam is approximately 50 % elemental mercury by weight.

Mercury is a global pollutant of concern that is now being acted upon via the United Nations (UN) Minamata Convention of which Canada is a signatory. Worldwide an estimated 5,500 to 8,900 tons of mercury enters the atmosphere each year.[117] Much of this mercury is released due to anthropogenic activities, and this includes cremation that may be attributable to dental amalgams (0.2 % of global releases). In Canada, total mercury emissions in 2010 were estimated to be 4,470 kg per year (less than 0.1% of global releases), of which 91 kg was attributable to cremation (release from cremation is assumed to be mainly from dental amalgam[117]).

Whereas the amount of mercury released from the Canadian dental sector is relatively small on a global scale, environmental and human health concerns exist, as mercury is firmly established to be persistent, toxic, and bioaccumulative.

All forms of mercury are innately toxic, although the chemical form of mercury is critical in understanding its environmental fate and ultimately its risk. In the dental clinic, elemental mercury is used; although upon release into the environment it is oxidized to inorganic mercury. As subsequently elaborated, this inorganic mercury can be released into the waste water stream and, eventually, the broader aquatic ecosystem. Within aquatic ecosystems, inorganic forms of mercury can be methylated by certain bacteria into methylmercury. This is noteworthy, as methylmercury (unlike the other forms of mercury) is bioavailable and biomagnifies two to 10 times in fish and shellfish.[10] Consumption of contaminated fish and shellfish is the main source of mercury exposure to most human populations and many wildlife, and there is ample evidence of exposure-related adverse health outcomes in these species.[118,119] In Canada the issue of mercury contamination is a particularly sensitive one.[10] For example, fish consumption guidelines exist in many jurisdictions, thus impacting sport and recreational fishing opportunities for many Canadians. As well, key traditional or country foods consumed by First Nations and Inuit communities are often contaminated with unsafe amounts of mercury.[10]

The *Canadian Environmental Protection Act* designates mercury and its compounds as toxic substances under Schedule 1, and the chemical is also covered nationally under the *Fisheries Act*, the *Hazardous Products Act*, and Canadian Food Inspection Agency guidelines. The Canadian Council of Ministers of the Environment, or CCME, has determined that environmental levels of mercury across Canada warrant efforts to reduce atmospheric and waterborne emissions of mercury and mercury compounds derived from both deliberate uses (such as in dentistry) and from incidental releases. At the provincial and municipality levels, there also exist various pieces of legislation and bylaws limiting mercury releases into the environment.

Dental Amalgam — Exposure Assessment

As abovementioned, contamination of aquatic ecosystems by mercury is the main route of exposure to most human populations and many wildlife species. Given that several sources of mercury exist across Canada, and that both Canada and the dental sector are relatively small contributors, here we aimed to estimate just how much mercury was being discharged into aquatic ecosystems by the Canadian dental sector. To achieve this, we adapted calculations performed in the US, in a study that was sponsored by the American Dental Association.[120] The calculations performed here for Canada rely upon several inputs and assumptions detailed in the aforementioned US-based report, and are supplemented with Canadian figures, when possible. According to the Canadian Dental Association,[83] there were 19,563 licensed dentists in the country in 2010. Of these, approximately 89% (n = 17,411) were in general practice. From the US study, we assumed that 76% of these

dentists (n = 13,232) used amalgam. The remaining 11% of Canadian dentists were assumed to be specialists. Of these specialists, it was assumed by the American Dental Association that pediatric dentists, prosthodontists, and endodontists only use amalgam and that these dentists comprise approximately 35% of all specialists. Thus, in Canada we estimated that there were 750 of these particular specialists, and conservatively estimated that all of these individuals used amalgam.

In the US, it was estimated in 1999 that general dentists placed 713 restorations per year and that specialty dentists placed 440 restorations per year. Applying these numbers to Canadian results in an estimated 9,764,521 (approximately 9.8 million) restorations placed per year, although this number is likely overestimated given the declining use of amalgams. Assuming that the average mercury content in a double spill of amalgam is approximately 450 mg,[120] here we estimated that 4.4 metric tons of mercury (4,394.1 kg) are used annually in the Canadian dental sector. We note, however, a footnote on page 3 of a report by the Canadian Council of Ministers of the Environment that "approximately 1.3 tonnes per year of mercury in new filling material is placed each year in the mouths of Canadians…"[101]

Not all the amalgam is used during placements, and the leftover ("non-contact") amalgam waste can range from 15% to 50%.[120] Using 25% as an approximate value, we estimated that 1.1 metric tons of non-contact amalgam waste was generated that could be recycled. During the placement process, it was estimated that approximately 30 mg of mercury per placement was lost to a dental clinic's waste water system, and thus across Canada this would amount to approximately 292.9 kg per year of mercury.

Mercury may also be lost when amalgams are removed. In Ontario,[121] it was estimated in 2002 that general dentists removed an average of 412 amalgams per year (versus 710 per year and 440 per year in the US by general and specialty dentists, respectively.[120] Scaling the Ontario numbers across Canada resulted in an estimated 5,760,682 (approximately 5.8 million) amalgams being removed per year by general and specialty dentists. The US study estimated the average mercury content in a removed amalgam to be approximately 300 mg and that 90% of this mercury would be released into a clinic's waste water system. Thus, we estimate that approximately 1.6 metric tons (1,555kg) of mercury would be discharged each year into a clinic's waste water system during the removal of amalgams.

To summarize all of the aforementioned, we estimated that mercury discharge from amalgam placements (292.9 kg per year) and removals (1,555 kg per year) into internal waste water systems of dental clinics in Canada total 1,848 kg per year. This is in alignment with a footnote on page 3 of a report by the Canadian Council of Ministers of the Environment that mentions "a report for Environment Canada… suggests as much as 2 tonnes per year may be generated." We also note that these estimates reflect data and assumptions that may be approximately 15 to 20 years old, and with the declining use of amalgam that the actual values now may be lower.

The Canadian Council of Ministers of the Environment have established a national standard to aid in the reduction of dental amalgam waste into the environment.[101] As indicated previously, we calculated the amount of mercury generated from the placement and removal of amalgam. While some of this mercury may be captured through chairside traps and vacuum filters, a substantial amount of mercury may be released into the public sewage system without added protections. The US study[120] estimated that clinics with both a chairside trap and a vacuum filter captured approximately 81% of the amalgam. Amalgam separators have emerged as a practical and affordable technology to capture mercury

within clinics (e.g., those compliant with ISO 11143:2008 achieve at least a 95% removal efficiency).[122]

In Ontario, a 2002 study estimated that 22% of clinics in the province had amalgam separators and that these were 98.9% efficient,[121] although a more recent national assessment by Environment Canada[12] of 1,250 dental clinics polled found that 97% of them were equipped with ISO-certified amalgam separators. Based on this, we estimated that the amount of mercury captured within the clinic would be 1,848 kg of mercury per year, thus leaving 30.3 kg per year left for discharge into the sewage system. Earlier estimates for Canada by two consulting firms (i.e., 686 kg per year, O'Connor Associates Environmental Inc.; 781 kg per year, CC Doiron & Associates) were higher, although we noted that these earlier estimates (approximately in the late 1990s) may not have considered the ubiquity of amalgam-separating technologies. Also, the aforementioned Environment Canada survey from 2012[12] calculated that 75 kg of mercury was released (down from 1,879 kg in 2000) from dental clinics, although we were unable to review that particular report to compare our methodologies. Nonetheless, both calculations showed levels to be much lower than previously estimated.

Potential environmental risks need to consider the amount of mercury that is ultimately released into surface waters. Assuming that the mercury capture efficiency of sewage treatment plants is 95% based on a US study,[121] here we estimated that 1.5 kg of mercury per year (of the 30.3 kg per year released into the sewage system) would be discharged into Canadian surface waters. Some of the mercury captured by the sewage treatment plant would be removed as grit solids or biosolids. Using inputs and calculations outlined in the US study,[121] we estimated that an additional 1 kg of mercury may be released into surface waters following the incineration of some biosolid waste. In total, we estimated that 2.5 kg of mercury per year ultimately flows into Canadian surface waters as a result of amalgam usage. To put this into context, the 2013 UNEP Global Mercury Assessment calculations for Canada estimated mercury releases across the country to be 4,470 kg per year.

Dental Amalgam — Toxicology

As noted previously, a limitation in the work is that toxicological studies (like exposure assessments) have largely focused on chemicals within amalgam, like mercury and not the amalgam itself; the discussion here, therefore, is focused generally on mercury and not dental amalgam specifically. The amount of mercury entering Canadian aquatic ecosystems as a result of amalgam use is relatively small. Aside from one study on goldfish,[123] we were not able to identify studies that specifically characterized the potential toxicity of amalgam-related mercury releases toward an ecological receptor. Nonetheless, there is a robust body of literature documenting the environmental impacts of mercury toward a range of biotic receptors in the Canadian environment;[10] hence, the overall concern as exemplified by a global policy instrument (Minamata Convention). It has been established that all forms of mercury are toxic and that, in particular, they disrupt the structure and function of the nervous system.[116] Across Canada, there have been case reports of mercury-poisoned fish, birds, and mammals, and these were related to past exposures to relatively high levels of mercury.[10] Nowadays, such exposures are rare, although there is strong scientific consensus that chronic exposure of fish and wildlife to relatively low levels of mercury is associated with subtle, yet ecologically meaningful, changes in reproduction and behaviour.[10]

Composite Resins

Composite Resins — Hazard Identification and Toxicity

The use of amalgam as a dental filling material is declining and being substituted with a range of alternate restorative materials.[124] The major types of alternate restorative dental materials include composites and glass ionomers. Despite possible benefits, the general consensus, consistent with the findings of the CADTH clinical review, is that these alternate materials are more expensive than amalgam and less durable. Furthermore, the safety of these materials has not been well-studied and is further complicated because the chemical composition can vary. While these materials contain chemicals that are known to be toxic, the environmental fate of the chemicals in these materials as well as their exposure routes and adverse effects toward human and environmental health are poorly understood.[124] As such, the lack of information and data negates the possibility to perform a detailed evidence-based environmental risk assessment of such materials.

For resin-based composites in particular, a number of chemicals have been identified that may be released during the restoration's life cycle, from manufacturing to placement, to removal and disposal. These chemicals are largely monomers and include chemicals like 2-hydroxyethyl methacrylate, triethylene glycol dimethacrylate, or BPA-derived monomers such as BPA-GMA. Except for BPA, there is limited information on the other chemicals (either as single chemicals, or more relevant as mixtures) in terms of potential exposures, hazards, and risks.

The toxicology of BPA has been thoroughly reviewed by several expert committees, including a Food and Agriculture Organization of the United Nations/WHO group.[27] There is ample evidence of toxicity from animal studies, and a growing body of epidemiological data pointing to exposure-related adverse effects in neuro-development and reproductive health. Once in the environment, BPA can degrade relatively quickly, although continual source inputs mean that ecosystem components, including fish and wildlife, can be chronically exposed. Societal and scientific concerns related to BPA motivated the Canadian government to include the chemical in Batch 2 of its Chemicals Management Plan, following which it was concluded that exposures to BPA be kept as low as possible, especially for newborns and infants.

Composite Resins — Exposure Assessment

Concerning BPA, given its endocrine-disrupting properties, there have been concerns about exposures within the Canadian population. For example, the 2007-2009 Canadian Health Measures Survey revealed that 91% of the population had detectable urinary BPA levels with an average measured level of 1.2 mcg/L,[125] although this is almost 50% of what was found across the US via their National Health and Nutrition Examination Survey. A number of BPA sources exist (mainly contaminated food and water), and while this can include composite resins, the dental community organizations such as the American Dental Association and US FDA conclude that there is no threat to human health from its use in restorations.[126] For example, Kingman et al. found that BPA levels in the saliva and urine of patients increased after restoration placement, but these levels returned to baseline within approximately one day of placement.[127]

While the potential environmental effects of BPA are numerous, and despite some initial studies to understand releases, unlike our assessment abovementioned for mercury , there is limited information to able to calculate how much BPA enters the environment from dentistry and ultimately causes risk to fish and wildlife.[128]. The BPA content of composites is

not clear, nor is its fate and bioavailability in ecosystems. Nonetheless, Environment and Climate Change Canada, along with Health Canada, have concluded that “BPA is entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity and that constitute or may constitute a danger in Canada to human life or health.”[129] In the aforementioned federal environmental quality guideline for BPA, environmental measurements (e.g., levels in water and sediment) of the chemical across Canada are reported upon and related to guidance values.

Summary of Results

The dental profession relies on a variety of materials and processes to restore the anatomy and function of teeth, although these are not without some risk to the environment. Our review focused on the environmental risks associated with the two main restorative materials used in dentistry —amalgam and composite resins. In particular, we note that a detailed comparison of these two materials is not possible given the lack of focused studies on the matter. For amalgam, the presence of mercury has been of concern for decades. While mercury has been established as a chemical that is persistent, bioaccumulative, and toxic, the relative small contribution of mercury into the Canadian ecosystem from use in dentistry, as well as the over-time declines in its use, suggest that the potential impacts on the environment are much less than other sources. There is an increasing use of composite materials as dental fillings, although relatively little is known about the fate of these materials in the environment and downstream impacts on the ecosystem. Most attention and information is on BPA, and whereas this chemical has been shown to contaminate ecosystems and disrupt fish and wildlife health, linking potential impacts back to the Canadian dental sector is not possible with the current state of knowledge.

Ethics

The purpose of this analysis is to identify and reflect upon key ethical, legal, and social considerations relevant to addressing the central policy question of this HTA, namely: Should dental amalgam continue to be used in Canada? This question is a natural follow-up to the UNEP Minamata Convention on Mercury, which proposes a phase-down of mercury by national governments according to local needs (Table 18).[130,131] Whereas the other sections of this HTA often touch upon broadly ethical concerns, the aim of this analysis is to make such issues explicit and to identify others that may be relevant to any recommendations regarding the continued use of dental amalgam in Canada.

The issues raised in this section necessarily go beyond narrowly defined ethical concerns to encompass broader legal and social considerations. It is common in the ethics literature, across a broad range of health-related issues, to refer to ethical, legal, and social issues(ELSI) when addressing broader values-related considerations. Hence, this discussion will touch upon broader historical, social, and legal considerations that serve to shape and inform the ethical issues identified.

The aim of this analysis is to address research question 9: What are the ethical issues associated with the use of dental amalgams compared with the use of composite resin restorations?

Considering the way in which dental services are provided and covered in Canada and the general ethical issues motivating this HTA, there are several broad ethical questions to consider when comparing amalgam with composites:

- What is the appropriate balance between government oversight and intervention versus individual control and/or responsibility (for both providers and recipients) regarding the choice between amalgams or composites?
- How do we balance competing values in this regard (e.g., financial costs, aesthetic preference, health and safety, environmental protection)?
- Does the manner in which dental care is funded (i.e., through private or public insurance) affect the manner in which various value preferences and concomitant ethical concerns are characterized and addressed?

These and other ELSI-related questions will guide the analysis that follows.

The analysis of ELSIs for this HTA presents a number of unique challenges due in no small part to the protracted nature of the amalgam debate. A historical overview of the amalgam debate is provided in Appendix 20. Although dental amalgam has been used in dentistry for more than 150 years, questions about its suitability as a restorative material have been continuous to the present day.[132-137]

The persistence of the issue presents particular challenges for the weighing of evidence and arguments regarding the use of amalgams. Society grants certain privileges to self-regulating professional bodies like dentistry (e.g., establishing admission standards, setting professional practice standards, enforcing discipline, etc.) based on the esoteric body of knowledge which members of the profession ostensibly hold. In return for granting such privileges, society expects professional bodies to exercise certain fiduciary responsibilities for the broader public good including the provision of safe and appropriate services. However, when there is strong and persistent disagreement about a key element of the knowledge base for which that profession is responsible, the public is understandably

confused and potentially vulnerable. Such is the case with dental amalgam as the knowledge claims of those on either side of the debate are dismissed and/or disputed by those who hold the contrary view, even as each side often questions the integrity and/or the professional competency of the other.[138-145] When such matters cannot be sorted satisfactorily within a professional body, they often find their way into the courts, as evidenced by numerous legal challenges in various jurisdictions throughout the past several decades.[146-152]

We will explore some of these ongoing tensions, challenges, and controversies in what follows, in order to identify an ethically sound way forward for Canada regarding the use of dental amalgam.

Methods

This ELSI analysis draws on the other sections of the HTA that have systematically reviewed the literature on various aspects of the dental amalgam versus composite resins issue. The Clinical Review, Economic Evaluation, Patients' Perspectives and Experiences Review, Implementation Issues, and the Environmental Impact sections of this report have analyzed available evidence according to prescribed selection criteria; insofar as that evidence base serves to highlight relevant ELSI germane to this discussion, the present analysis draws upon those reviews. However, whereas other sections of this HTA have been purposively narrow in their selection criteria, generally focusing on literature from the recent past and, in some cases, drawing materials primarily from the North American context so as to approximate the Canadian situation, the literature search for this ELSI review has been purposely broad. This is due in part to the historical nature of the amalgam debate that has been ongoing for the better part of a century and a half. Inasmuch as ELSI reviews are primarily about values which evolve, take shape, and become engrained over long periods of time, a longer perspective is necessary. Values are informed by facts, but they are also subject to pressure from political, cultural, and other social forces.[153-155] The fact that the concerns with amalgam use have been raised not only in North America and Europe but in other industrialized and developing nations, as well,[156-163] is important to a general understanding and appreciation of how firmly entrenched attitudes and values have become around the amalgam issue throughout a large part of the industrialized world. Indeed, major international bodies such as the WHO and the Fédération dentaire internationale (FDI) have issued joint statements throughout the years on the amalgam issue.[164-166] Hence, a much broader literature review was undertaken in order to laying bare some of the deep and persistent features of the ongoing amalgam debate. (See Appendix 20 for a brief summary of this historical debate.) Given this broader purview, this ELSI section raises issues (particularly with regard to amalgam toxicity) that have been largely settled in mainstream dentistry in North America but which are either still ongoing or have resulted in different outcomes, with greater restrictions on the use of amalgam, in other parts of the world. Hence, the discussion of issues and recommendations in this ELSI section will at times take into account scientific opinions and social perspectives not reflected directly or in the same manner in other sections of the report that found amalgam to be generally safe and more effective when compared with composite resin.

Literature Search

The literature search was performed by an information specialist, using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with Epub ahead of print, In-Process records and daily update, via Ovid and Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dental amalgams and composite resins. The search strategy for the dental amalgam and composite resin concepts were based on the search strategy for question 2.

Methodological filters were applied to limit retrieval to studies related to ethical, legal, and social issues. Retrieval was not limited by publication year but was limited to the English or French language. The search strategy is available upon request.

The search was completed on July 18, 2017. Monthly alerts were established to update the searches until February 1, 2018. Studies identified in the alerts and meeting the selection criteria of the review were incorporated into the analysis if they identified prior to the completion of the stakeholder feedback period of the final report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economic-related repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts.

In addition, the literature search examined a variety of other sources that were identified through a separate electronic search of articles from the ethics and clinical science literature. While addressing ELSI indirectly, these sources of information raised and/or shed light on a variety of ELSI issues related to the choice between amalgam and composite resins. Additional relevant literature was also found using less systematic searching of both indexed and grey literature sources.

Literature screening and selection

The selection of relevant literature proceeded in two stages. In the first stage, the title and abstracts of citations were screened for relevance by a single reviewer. Articles were categorized as "retrieve" or "do not retrieve," according to the following criteria:

- provides normative analysis of an ethical issue arising in the use of amalgams or resins when treating dental caries
- presents empirical research directly addressing an ethical issue arising in the use of amalgams or resins when treating dental caries
- explicitly identifies but does not analyze or investigate empirically an ethical issue arising in the use of amalgams or resins when treating dental caries.

The goal in a review of bioethics literature is to canvass what arises as an ethical issue from a broad range of relevant perspectives. As such, the quality of normative analysis did not figure in the article selection criteria; any identification of an issue by the public, patients, health care providers, researchers, or policy-makers was of interest whether or not it was presented through rigorous ethical argumentation. For example, academic ethicists may focus on certain issues related to theoretical trends in their discipline, while an opinion piece by a clinical or policy leader, or a patient, may bring to the fore ethical questions that are neglected by academic ethicists but are highly pertinent to the assessment of the technology in the relevant context. Despite the different standards of normative

argumentation for each kind of report, the importance of the issues raised cannot be assessed solely by these standards and so literature cannot be excluded based on methodological standards.

In the second stage, the full-text reports were reviewed by the same single reviewer. Reports that met the abovementioned criteria were included in the analysis and those that did not meet the criteria were excluded.

Analytic approach

This analysis draws most directly on two classic perspectives that are well-established in the health ethics literature; namely, the utilitarian/consequentialist approach, and the deontological/duty-based approach. The former focuses more directly on the overall consequences of particular courses of action and deals with questions of individual rights and duties, and considerations of social justice, only indirectly. Conversely, the deontological approach gives priority to considerations of individual rights and concomitant duties while treating overall utility (i.e., the greatest good for the greatest number) as of only secondary importance. Put otherwise, from a deontological perspective, the most important consequence is whether individual rights are properly honoured and accounted for irrespective of whether some supposedly greater good might be accomplished by ignoring or overriding the rights of certain individuals. While these two theoretical approaches are often treated as contrary, there is a well-established tradition within contemporary health care ethics that treats them as complementary.[167]

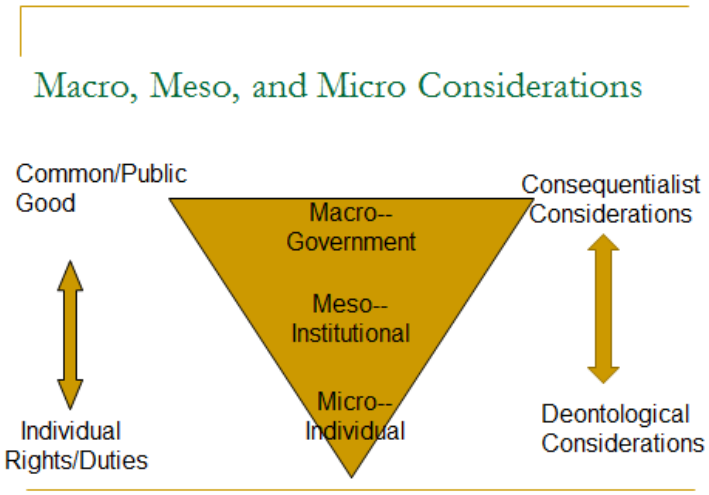
In practice, whether one relies primarily on consequentialist or deontological considerations is often dictated by the context in which a particular issue arises. Consequentialist considerations generally take priority in the public health domain, where the overall good of the population as a whole is the focus. In the current context, the broader public health concerns related to mercury contamination and the contribution of dental waste to this problem as reflected in the Minamata Convention are best viewed through a consequentialist lens. In the clinical context, on the other hand, the rights of individual patients to be informed about the nature of the materials that are being put into their mouths,[168,169] and the concomitant duties of dental professionals to provide that information in a clear and unbiased manner, are best viewed from a deontological perspective, which generally favours the rights of the individual over some perceived broader public good. This tension is particularly evident in the current context when attempting to balance the overall utility for society when making policy decisions about dental amalgam as opposed to the rights of individual citizens. If a policy decision was made to discontinue the use of dental amalgam because of environmental concerns, for example, this could undermine the individual dentist's or patient's right to use or choose a less-expensive and potentially more durable restorative material. Conversely, if a policy decision was made to continue the use of dental amalgam because of its perceived overall economic benefits based on reduced costs and greater durability, this would require that appropriate efforts be taken to respect the autonomous rights of individual patients to be informed of various restorative options, while placing concomitant duties on dentists to provide such information in an unbiased manner. This ELSI review aims to explore such values tensions and the factors that might inform one policy decision as opposed to another.

As the foregoing indicates, an ELSI analysis of dental amalgam versus composite resins raises a variety of issues. For the purposes of analysis and reporting, this broad range of issues will be divided into macro, meso, and micro concerns. Macro concerns are generally policy-related issues handled at a population level through legislation such as the *Canada*

Health Act or by a government agency such as Health Canada, Environment and Climate Change Canada, or related provincial ministries. In the current case, the Minamata Convention pushes such macro concerns to the level of international law. Meso level considerations are those that concern mid-level institutions and bodies. The Canadian Dental Association is an example of a meso level entity, as are various municipal authorities that are at times tasked with implementing environmental policy decisions in the local context. At the micro level, we consider the impact that various policy options for dental amalgam would have on individual patients and/or practitioners.

Figure 5 illustrates the analytic process and the dynamic relationship between consequentialist and deontological considerations. The inverted pyramid captures the idea that the issues under consideration range from broad public policy concerns to more narrow concerns of individual patients and practitioners.

Figure 5: Levels of Decision-Making and Types of Ethical Considerations



While the foregoing has singled out consequentialist and deontological ethical perspectives as particularly relevant to the ELSI analysis offered here, other ethical perspectives will occasionally inform elements of this discussion. Virtue theory, for example, focuses on desirable qualities of character that contribute to virtuous persons and professions.[167] Insofar as elements of this discussion bear on the character of various professional bodies and/or the individuals that comprise those bodies, considerations of virtue may be relevant.

Results

Literature Search and Selection

The literature search yielded 913 records. After removing duplicates, reviewing record abstracts, and appraising full--text articles of potentially relevant articles from both the database search and supplemental searches, 347 articles were selected for close reading and analysis. Of these, a total of 14 articles were identified that explicitly acknowledge ethics related to the use of amalgam or composite dental restorations.[170-183] See Appendix 19 for a flow chart describing the literature search and selection process. No

single article completely answered the research questions and none compared the overall risks and benefits of amalgam and composite resin dental restorations.

Analysis

Macro-Level Issues

Macro-level ELSI analyses draw upon utilitarian/consequentialist ethics models that emphasize the overall good for society as a whole when setting social policy. Overarching political bodies and their agencies are generally the entities responsible for determining what constitutes the general social good in any given sphere, and for establishing laws and/or promoting social policies designed to achieve those ends. While concerns regarding individual rights generally do not figure prominently in macro-level analyses, broader issues of social justice that may run contrary to direct utilitarian calculations may be relevant.

Environmental Concerns

Although the debate regarding the safety of dental amalgam as a restorative material continues as far as its clinical utility is concerned, the contribution of dental amalgam to overall environmental load of mercury has emerged as one aspect of that controversy where some semblance of a consensus has emerged (Appendix 20). As a signatory to the UNEP Minamata Convention, the government of Canada has adopted a macro-level policy that keeps the country in step with the international community, while aiming to ensure that Canadian citizens are appropriately protected in accordance with its ethical obligations to both protect the environment while promoting public health. The Minamata Convention contains nine recommendations regarding dental amalgam (Table 18), all of which are germane to particular ELSI. While Canada had met the minimal requirements for Minamata (i.e., implementing at least two of nine recommendations) even before the Convention was ratified, the Convention instructs national governments to implement the recommendations "according to local need." Supposedly, countries with less-developed dental care systems would not be capable of implementing all nine recommendations in the near term, and hence would be expected to meet only the minimal requirement. Developed nations like Canada, on the other hand, who have already met the minimal requirement, would have a stronger ethical obligation to implement as many of the recommendations as is reasonable, given the Canadian context. In this respect, one would expect that Minamata would have a continuing impact on Canadian dental care, some of which are addressed in the body of this report.

Table 18: Dental Provisions of the Minamata Convention

Part II: Products subject to Article 4, paragraph 3

Mercury-added products	Provisions
Dental amalgam	Measures to be taken by a Party to phase down the use of dental amalgam shall take into account the Party's domestic circumstances and relevant international guidance and shall include two or more of the measures from the following list: (i) Setting national objectives aiming at dental caries prevention and health promotion, thereby minimizing the need for dental restoration; (ii) Setting national objectives aiming at minimizing its use; (iii) Promoting the use of cost-effective and clinically effective mercury-free alternatives for dental restoration; (iv) Promoting research and development of quality mercury-free materials for dental restoration; (v) Encouraging representative professional organizations and dental schools to educate and train dental professionals and students on the use of mercury-free dental restoration alternatives and on promoting best management practices; (vi) Discouraging insurance policies and programmes that favour dental amalgam use over mercury-free dental restoration; (vii) Encouraging insurance policies and programmes that favour the use of quality alternatives to dental amalgam for dental restoration; (viii) Restricting the use of dental amalgam to its encapsulated form; (ix) Promoting the use of best environmental practices in dental facilities to reduce releases of mercury and mercury compounds to water and land.

Source: From Minamata Convention on Mercury. New York: United Nations; 2013 Oct. Available from: https://treaties.un.org/doc/Treaties/2013/10/20131010%2011-16%20AM/CTC-XXVII-17.pdf. ©United Nations [2013]. [131]

The relatively small contribution of mercury into the Canadian ecosystem from its use in dentistry suggests that the potential impacts on the environment are much less than from other sources. (See the Environmental Impact section.) Nonetheless, throughout the past 15 years, Canada has taken significant steps to set a Canada-wide standard to reduce releases of mercury in waste amalgam from dental practices.[101] As of 2012, 97% of dental offices in Canada were following best management practices for amalgam disposal. (See the Implementation Issues section.)[12] Whereas the Minamata Convention includes provisions for the phase-down of amalgam, concerns have been raised that these provisions are voluntary and do not include binding targets. "... [T]he international community should begin exploring ways to strengthen the implementation of the dental amalgam treaty provisions," states one recent commentary, "by establishing binding phase-down targets and milestones as well as exploring financing mechanisms to support treaty measures."[184] It has been noted, for example, that whereas the use of amalgam separators are mandated, some may choose to forego them because of added costs. As noted in the review of implementation issues, not all practices in Nunavut are reported to have installed them. Inasmuch as concerns about mercury exposure are often exacerbated in First Nation's communities that rely more heavily on fish in their daily diets, this may be a particular area of concern.[185]

Public Funding of Dental Care

Public health policy is another macro-level instrument that can affect both the manner in which dental services are provided, as well as the choice of materials used for restorations.[186] The UNEP has observed that addressing imbalances in insurance schemes can contribute to the phase-down of amalgam use. Many European countries which have

introduced policies to either prohibit or significantly restrict the use of dental amalgam include either universal coverage of dental services or make other significant provisions for dental coverage.[187] A recent population-based study assessing factors that influenced dentists' choices of composite resin or amalgam in posterior direct restorations showed that choices were influenced by the type of payment available.[188] As noted elsewhere in this HTA, some government-funded provincial dental plans will cover only amalgam restorations in posterior teeth (see Implementation Issues).[108] Not only do such policies affect ongoing efforts to reduce amalgam use as it pertains to environmental concerns, but they restrict patients' (or consumers', depending on the view one takes) rights to make informed choices regarding the type of restorative materials that are placed in their mouths. Indeed, the Minamata Convention directs the parties to discourage insurance policies and programs that favour amalgam use over mercury-free dental restorations.[131]

In Canada, approximately 5% of dental services are publicly financed.[186] Addressing public funding of dental services will be especially important if efforts to reduce amalgam use are successful, as the increased costs associated with composite resins could prove prohibitive for many who require restorative treatment but are not covered through a public or private insurance plan. The right to individual choice is a strong moral norm in Canadian society (a point to which we will return in the micro level considerations of individual autonomy). Inasmuch as dental care is not included in the *Canada Health Act* and health care is a provincial responsibility in any case, close collaboration between the federal, provincial, and territorial governments will be necessary to effect positive oral health outcomes for all Canadians as a downstream effect of the Minamata Convention.

The dental profession in Canada has lobbied successfully throughout the years to protect and advance its own interests. For example, dentists argued successfully that it would be more cost-effective for government to limit the direct delivery of publicly financed dental care, allowing for its delivery through private clinics.[186] Pressure from the profession has also impacted the nature of publicly funded services in Canada, including payment for composite restorations in some provincial plans.[186] Such macro-level policies have important downstream consequences, as public fee schedules often pay less for amalgams, thus providing some provider incentive to use composites. Granted, there are other factors influencing the choice of materials, including what is most appropriate for the patient, and consumer preference for tooth-coloured restorative materials. Nevertheless, inasmuch as the risk of secondary caries is reported to be significantly higher with composites than with amalgams, as noted in the Clinical Review, composites may not be the most appropriate choice for high caries populations, which are often served through publicly financed programs (See also the Economic Impact section.)[186] On the other hand, public financing of alternative materials provides more options for individual consumers in their choice of restorative materials, whether for aesthetic or safety reasons. Nevertheless, the Minamata Convention encourages national entities to promote "cost-effective and clinically effective mercury-free alternatives..." (Table 18).[131]

Public Health Education and Information

Many, in the population, are poorly informed or simply unaware of the existing information (environmental or otherwise) related to amalgam use.[187] One recommendation endorsed by Health Canada's stakeholder panel in 1996 was that "a public and professional information package be prepared to make the public more capable... of making informed dental health choices."[19] Health Canada and Environment and Climate Change Canada might consider combining efforts to raise public awareness of environmental mercury concerns in general, and of the contribution to the environmental load contributed both from dental amalgam

waste and from persons with amalgam fillings through human waste (feces and urine), crematoria, etc.[136,187] Another means of raising public awareness might include a link on the Public Health Agency of Canada website that vets and posts links to current research so that the consuming public has access to reliable sources of information on the evidence related to amalgam safety and environmental toxicity.

Given the lack of consensus about what would constitute sufficient evidence of safe or unsafe levels of mercury exposure from dental amalgams, various professional bodies with differing views may be unable to provide an impartial and comprehensive overview of all the available evidence. It is therefore incumbent on the macro-level institutions represented by government to ensure the consuming public has ready access to the full range of scientific evidence on the subject presented in an impartial, comprehensible, and readily accessible manner. Indeed, the current HTA might be viewed as a macro-level effort to address the micro level needs of the Canadian population in this regard. Some states and municipalities in the US provide "fact sheets" that dentists are required to provide to patients,[174] and a number of US states have enacted informed consent legislation.[189] Inasmuch as all Canadian provinces require dentists to obtain informed consent, it may be necessary for provincial governments and various regulatory bodies to monitor informed consent practices and/or take steps to ensure informed consent is obtained regardless of the material used.

With the trend toward a lower use of amalgam — whether out of environmental, aesthetic, or personal health preferences on the part of consumers — there is a continuing need for alternative restorative materials. Although it does not figure centrally in the current analysis, safety issues related to composite resins factor into this discussion, as well.[190-193] One of the recommendations of the Minamata Convention is that parties promote research and development of quality mercury-free materials for dental restorations.[131] To that end, Canada's major research bodies might earmark additional research funding to expedite efforts in the continuing development of safe, effective, and economically viable restorative materials.

Federal Funding of Research

Finally, given the persistent questions about amalgam safety, Canada might consider leveraging current research efforts to cast further light on these issues. For example, the Canadian Longitudinal Study on Aging is currently following some 50,000 Canadian men and women between the ages of 45 and 85 for at least 20 years from the time of recruitment, with a view to understanding the development of health and disease during the aging process.[194] Collecting baseline information about dental health, the number and types of fillings, etc., might provide basic epidemiological data to inform ongoing research for mercury toxicity and potential associations with other chronic illnesses.

Meso-Level Issues

Role Ambiguity of Dental Professionals

Many of the meso level ELSI related to the amalgam question hinge on the role of dentistry within the Canadian context and the extent to which members of the profession portray and conduct themselves as either health care professionals or as business entrepreneurs.[186] The role can be ambiguous both within the dental profession and for the public at large. On the one hand, dentists portray themselves as health professionals, providing an essential health care service.[195] In exchange for the privilege of self-regulation, dental professionals bear certain fiduciary responsibilities including putting patient interests over self-interest.[145,168] On the other hand, the majority of dentists are in private practice with the

primary aim of operating a successful enterprise.[157,186] As such, as discussed in the review of implementation issues, "cost considerations, margins of profit, and efficiency of practice are important parameters that contribute to decision-making regarding choice of material." This role ambiguity can affect patient/client interests.

Financial Conflicts of Interest

The issue of financial conflicts of interest has figured prominently in the amalgam controversy from the outset, with each side accusing the other of opportunistically taking advantage of a vulnerable and unsuspecting public. (See Appendix 20 for an historical overview.) In the 1990s, dental associations in both the US and Canada addressed the emerging issue of dentists, apparently taking advantage of patient's perceived anxieties about amalgam toxicity by offering to replace them with composites.[139,141,196] Amalgam supporters argue that their continued defense of amalgam effectively cost them billions in lost income had they simply remained silent on the issue and joined in the practice of removing and replacing serviceable amalgams.[177,197] However, not all dentists who oppose amalgam have done so out of economic self-interest, citing reasons including ongoing concerns about amalgam toxicity (Appendix 20).

Professional bodies like the American Dental Association and the Canadian Dental Association have consistently lobbied for the continued use of amalgam.[177,198] As composite technology has been perfected, and dental schools have focused more on the latest techniques in training the next generation of practitioners, the ability to place composites more quickly has advanced. At the same time, patients/consumers have increasingly demanded composites for aesthetic reasons.[199] Another recommendation of the Minamata Convention is that representative professional organizations and dental schools should be encouraged to educate and train dental professionals on the use of mercury-free dental restoration alternatives and on promoting best management practices (Table 18). As noted in the Implementation Issues section, dental schools in Canada have been in compliance with this recommendation for some time.

Clear Communication

There is much ambiguity in the messaging being sent to patients/consumers regarding amalgam safety. Although the term "silver amalgam" is technically correct in that "amalgam" is simply an alloy of mercury with another metal, many consumers may not be aware of the relative ratio of mercury to silver in the restorative materials being placed in their mouths. Thus, while "silver amalgam" may be an accurate description for the technically informed professional, it could be misleading for a technically uninformed lay person. The term "dental amalgam" may therefore be preferable to "silver amalgam" for purposes of lay communication.

On the one hand, patients are often told there are no mercury related health concerns for dentists or their patients (implementation issues). On the other hand, dentists are instructed in "modern and safe methods of handling... and disposing excess mercury" such that "exposure to mercury for dental practitioners is minimal" (implementation issues).[179] If there are no health concerns when mercury is used in dental amalgam (i.e., Hg is not in its "pure state"), some have questioned why dentists must take special precautions in handling it.[140,143,200] In a similar vein, Health Canada's position statement on dental amalgams states that current evidence does not link ill health with amalgam. Nevertheless, on the basis of the precautionary principle, which is often invoked "in circumstances where there is some evidence that a particular activity may result in health or ecosystem damage, but great uncertainty as to the potential magnitude or nature of those impacts," [182] Health Canada

cautions against using amalgam with young children, pregnant women, and patients with impaired kidney function. For the lay public, this could be taken as implying there is some concern that some vulnerable populations could be at risk.[182,201]

The Canadian Dental Association has long recognized its ethical obligation to provide accurate and complete information to the consuming public including "an obligation to inform patients of possible concerns."[168] Inasmuch as there are alternative restorative materials available, even though current evidence has not established a clear link between amalgam and ill health, the consuming public has a right to be informed about any open questions regarding the safety and potential toxicity of all restorative materials so as to make fully informed choices. The establishment of adequate standards of information disclosure by regulatory authorities, if currently not in existence, and monitoring and maintaining those standards, would help ensure clear communication and informed public choice.

Irrespective of the patient safety issues, the continuing use of dental amalgam contributes to the global demand for mercury.[202] In light of the Minamata Convention, it is incumbent on the dental profession to support the use of alternative materials, while reducing the use of amalgam except in exceptional circumstances.[131]

Micro Level Considerations

Informed Consent

ELSI considerations at the micro level focus more directly on issues of individual rights and responsibilities. The primary concern in this regard is the patient's/consumer's right to make informed decisions about the restorative materials that will be placed in (or alternatively, removed from) their mouths, and the concomitant duties on the part of dental professionals to fully inform their patients/clients and to honour their patient's/client's informed decisions.[19,169,203] Given the potential toxicity of both the restorative materials under review (whether amalgam or composite resins), regulatory authorities should ensure an adequate standard of information disclosure is established where it does not already exist. A related micro level issue involves the individual dentist's right to conscientious refusal in fulfilling individual patient/consumer requests that the dentist believes could be harmful to the patient.[174]

The ethical principle of respect for autonomy underlies the doctrine of informed consent. However, the standard of information disclosure necessary to fulfill an ethical obligation in this regard is contingent on the context in which the matter of consent arises. Here again, the fact that individual dentists conduct themselves both as health care professionals and as profit-making businesses is relevant, as the standard of information disclosure necessary to fulfill informed consent requirements differs between business and health care environments.

In a business relationship, both seller and buyer are understood to be looking out for their economic self-interests. In this context, the seller meets their autonomy obligations by fairly representing the nature of the product being sold. The purchaser has a concomitant responsibility to protect their own autonomy by becoming an informed consumer. In the health care environment, however, an unequal level of knowledge is assumed between professional and patient such that the professional bears a fiduciary responsibility to ensure the patient is fully informed about any products or interventions on offer. The patient, by comparison, has a lesser obligation to positively advance their autonomy by virtue of the relative ignorance they have vis-à-vis the professional practice.[175]

Historically the dental profession in North America has struggled with the matter of patient autonomy and informed consent. In the 1990s, when public concerns about amalgam safety were on the rise, some dentists questioned the need to respect patient autonomy. "Autonomy could be dangerous" argues one commentator, if a dentist removes a serviceable filling because a patient requests it out of supposed misplaced concerns regarding safety.[171,204] Another argues that informed consent should not apply to amalgams, as they do not represent a significant risk.[205] Yet another advises that if patients ask whether mercury is poisonous, they should be told that, when combined with other metals, as in dental amalgam, mercury becomes "biologically inactive."[206]

Professional codes continue to emphasize the importance of informed consent.[195,207,208] However, some individuals question whether the profession is meeting its legal and ethical obligations in this regard. One legal scholar argues: "... the dental profession has basically ignored its duty to disclose material risks and has taken overt measures to ban its members from discussing potential risks with patients."[138] One US commentator suggests that federal and state legislation should be passed to ensure that consent forms are given to patients receiving amalgam restorations.[172] Inasmuch as the Canadian Dental Association has no regulatory authority, provincial legislatures may need to consider action in this regard as well, regardless of the material used. The standard of information disclosure for health care practitioners in Canada was established in Reibl v. Hughes in what is now known as the "modified objective test."[209] Essentially, this means that a health professional can neither rely on the common practice within the profession as it pertains to information disclosure (i.e., "the professional practice standard"), nor can they rely on a standard that divulges as much information as a hypothetical "reasonable person" would expect to receive (i.e., "the reasonable person standard"). Instead, Reibl v. Hughes established that the health professional must disclose as much information as a reasonable person in the patient's situation would need in order to make an informed decision ('the modified objective test'). This standard puts the onus on the health professional to know something of the individual patient's current circumstances in discussing various health options so as to tailor the information accordingly. With the expansion of genetic testing and the advent of "personalized medicine," this could have implications for informed consent for dental services. That is, if genetic research identifies certain genetic profiles that predispose some patients to a higher sensitivity to amalgam, for example, or that establish a connection between certain genetic profiles, mercury exposure, and the development of some chronic illnesses,[210,211] it may be incumbent on dental professionals to inform patients of such potential risks and/or recommend genetic testing for those with a family history that includes certain chronic conditions.

Herein lies the conundrum with informed consent for dental consumers. Given dentistry's ambiguous role as either health care profession or commercial enterprise, and given the ongoing concerns expressed in some quarters about the long-term safety of amalgam (see Appendix 20 for example, where the decisions of a number of European countries to eliminate the use of amalgam are documented), it is unlikely that there will be wide agreement any time soon on either standards of information disclosure, or on what constitutes fully informed consent for patients/consumers regarding restorative materials. The following representative sample of statements summarizes the tension nicely: "As of now, there is no credible, valid scientific evidence that dental amalgam harms humans other than those who might be allergic to its contents. To suggest otherwise is not true and, therefore, unethical."[176] Alternatively, "In the past 10 years research has shown that the amount of mercury released is more than previously believed, and that amalgams contribute to a person's overall exposure to mercury."[182] Finally, "Although the issue of amalgam safety

is still under debate, the preponderance of evidence suggests that Hg [i.e., mercury] exposure from dental amalgams may cause or contribute to many chronic conditions."[212]

Conscientious Refusal

Another micro level issue closely related to the matter of informed consent concerns the question of conscientious refusal on the part of dentists in complying with patient's requests. Here, again, the matter of professional role versus business relationship affects when and how this right (or responsibility) on the part of the dentist is interpreted and exercised. Professional codes generally advise dentists that the best interests of the patient are paramount, and that they are not obligated to do anything they believe is not in the best interests of their patients, even if the patient insists.[174] This ostensibly was the underlying rationale for the resistance to patient autonomy noted earlier in this discussion, and serves, as well, as the justification for American Dental Association and Canadian Dental Association policies that restrict dentists from removing and replacing amalgams out of perceived safety concerns on the part of patients (See Appendix 20). Assuming that the majority of dentists do have the best interests of their patients in mind, the conscientious refusal to do something they believe is a potential harm to their patient is understandable and morally defensible. However, this is true of dentists on either side of the amalgam debate.

Stigmatization of Patients

Finally, the matter of stigmatization as it relates to patients who believe their chronic health problems could be related to amalgam fillings is another micro level concern. (See Patients' Perspectives and Experiences.) Patients with otherwise unexplainable symptoms such as chronic fatigue or fibromyalgia are often labelled as hypochondriacs, as suffering from mental illness, etc.[213-218] It has been suggested that closer collaboration between physicians and dental professionals might lead to greater insights on a variety of intractable health issues.[99] All patients deserve to be treated with respect, irrespective of the opinions of individual practitioners. At the very least, given the intractable differences of opinion on amalgam safety and its potential concomitant health effects, dentists might be advised to refer recalcitrant patients if they themselves feel uncomfortable with those discussions.

Summary of Results

The ELSI analysis has identified a range of issues which can broadly be divided into macro, meso, and micro concerns. A summary of these issues and how they might be addressed by policy- makers or dental professionals follow.

Table 19: A Summary of Issues Regarding Dental Amalgam and Composites

Macro-Level Issues	
Environmental Concerns	There is a broad consensus about the need to reduce the environmental impact of mercury from all sources, including dental amalgam. Canada's decision to be a signatory to the UNEP Minamata Convention is an appropriate macro-level policy response in this regard. As a follow-up to the Minamata Convention, it is incumbent on the federal government to ensure that all dental practices comply with directives regarding the handling and disposal of amalgam waste. This could be particularly important for vulnerable populations in Canada's North.
Publich Health of Dental Care	The choice of restorative materials is affected by the manner in which dental services are funded. Although the amount of publicly funded dental care in Canada is relatively small, it affects the most vulnerable populations. Funding policies should neither unfairly restrict access to particular dental services nor affect individual patient choices of restorative materials — whether for environmental, aesthetic, safety, or other reasons.
Public Health Education/Information	The public should be properly educated about the environmental impacts of mercury from all sources, including the impact of dental amalgam waste. Up-to-date and accurate reporting on any safety-related issues is also necessary. In keeping with the Minamata Convention, the federal government should promote "cost-effective and clinically effective mercury-free alternatives..." for dental restorations.[131]
Federal Funding of Research	The Minamata Convention promotes the research and development of quality, Hg-free alternatives for dental restoration. Canada's major research funding agencies might earmark funds for ongoing research on alternative materials and on related health risks and concerns from all materials.
Meso Level Issues	
Role Ambiguity of Dental Professionals	The ambiguous nature of the primary role of the dental profession affects the nature of the professions' relationship with the consumer public, and the role of regulators vis-à-vis the dental profession (i.e., health promotion versus consumer protection). Such ambiguity has implications for other meso and micro level issues including professional responsibility, patient vulnerability, and consumer choice.
Financial Conflicts of Interest	Financial incentives may influence the choices of individual dentists in the recommendation and use of restorative materials. Patients/consumers may be vulnerable in this regard and deserve protection through appropriate government bodies. (See Macro-Level Issues.)
Clear Communication	The use of the term "silver amalgam," although technically accurate, could be misleading for an uninformed lay person. The term "dental amalgam" would be less confusing in this regard.
Micro Level Issues	
Informed Consent	The standard of information disclosure necessary to fulfill an ethical obligation to respect an autonomous right to make an informed choice differs between business and health care environments. Hence, the appropriate standard is related to the relationship between dental professionals and the public. (See Meso Level Issues.)
Conscientious Refusal	Any dental professional (irrespective of their view on amalgam safety) has the right to refuse to provide a service they genuinely believe to be a potential harm to the patient/consumer.
Stigmatization of Patients	Patients/consumers who explore the possible connection between amalgam and chronic health care conditions should be treated with respect and not stigmatized as malingerers, as mentally challenged, or otherwise maligned.

Hg = mercury; UNEP = United Nations Environment Programme.

Discussion

Summary of Overall Findings

The clinical review of efficacy was addressed by updating a 2014 Cochrane SR that identified seven eligible studies and meta-analyzed data from two of these; i.e., parallel-group RCTs describing 3,010 teeth in children ranging in age from six to 12 years at baseline.[6] Authors reported a statistically significantly higher risk of restoration failure (RR 1.89, 95% CI 1.52 to 2.35, $P < 0.001$) and secondary caries (RR 2.14; 95% CI, 1.67 to 2.74, $P < 0.001$) in composite resin versus amalgam restorations. A subgroup analysis of the remaining five split-mouth-designed RCTs (described by the 2014 Cochrane[6] SR authors has having "…major problems with the reporting of the data…") found similar results in restoration failure but no between-group difference in secondary caries. Our 2017 update identified one eligible split-mouth RCT published in 2016 that analyzed restoration performance in 40 teeth.[36] Because of the presentation of the data, these findings could not be pooled with data from primary analyses of the 2014 Cochrane SR. Authors of the 2016 RCT found zero events of restoration failure in both treatment arms, concluding that amalgam and composite resin restorations are both clinically acceptable.[36] Nonetheless, because of methodological limitations of the study identified in the update, the conclusions of the 2014 SR remain current.

Our *de novo* SR of the comparative safety of dental amalgam versus composite resin restorations identified 10 eligible reports representing three unique RCTs. Statistically significantly higher urinary Hg levels were reported among children with amalgam restorations in two trials through to five and six years of follow-up, respectively; although, levels in the amalgam groups did not exceed those reported to be toxic in the literature (i.e., 7 mcg/L[9]). Notably, urinary Hg levels were measured to seven years of follow-up in one of these two trials, and were no longer found to differ significantly between treatment groups.[44] Some statistically significant differences were observed between amalgam and composite resin groups using certain measures of renal, neuropsychological and psychosocial function, physical development, and post-operative sensitivity; however, the observed effects were inconsistent across outcomes, measures and/or time, favouring one or the other group either variably or inconsistently — suggesting the findings could have resulted from either a causal association or by chance. Finally, no statistically significant differences between treatment groups were observed in evaluations of neurological symptoms, immune function, and urinary porphyrin excretion. Importantly, an assessment of the risk of bias identified considerable risks of bias in all of the included studies and their reports, with some studies harbouring a risk of bias in more domains than other studies. Notably, all studies exhibited a risk of bias due to the inability of investigators to blind patients and research personnel, and often due to poorly reported methods and findings.

A cost-consequence model found that the useful life of a two- to three-surface posterior amalgam restoration exceeded that of a composite resin restoration. Likewise, the average Canadian cost for the first restoration and lifetime discounted costs for amalgam restorations were estimated to be lower than those for composite resin restorations. And while the use of amalgam incurs additional costs to dental clinics by way of the need for amalgam separators to manage waste, the time associated with the clinical placement of composite resin restorations is greater and likewise incurs additional costs.

The review of patient experiences was designed to integrate the experiences of patients with amalgam and/or composite resin restorations. However, a paucity of qualitative

research in this area resulted in the identification of four studies (reported in five papers) — none of which described any experiences with composite resin restorations. All included studies focused on patients with amalgam restorations and their experiences of perceived adverse reactions. Thematic analyses highlighted the patients' struggles to be understood and believed as they searched for a cause of their sense of ill health. Following from this, the experience of deamalgamation and detoxification was described as a difficult one that may not provide immediate health gain but provided some relief from the worry of a potential toxic influence on health.

The implementation review found that there are factors that influence the use of one type of restorative dental material over another. For instance, in Canada, there is no explicit policy in any jurisdiction that dictates the use of dental amalgam or resin composites. Notably, the majority of dentists in Canada are in private practice, where factors such as margin of profit and efficiency of practice are additional considerations and can affect the decision-making process for restorations. Nonetheless, dentistry education in universities does not appear to focus on one restoration over another, but dentists may choose to use materials that they are more comfortable with, that are newer and "more sophisticated," or that their supervising dentist primarily used. Importantly, geographic location (e.g., the north of Canada or remote communities) can be a factor and often limits available materials. Finally, patient profile and clinical indications are of concern to dentists when deciding on which restoration to use, as amalgam and resin composites have different mechanical properties that may be contraindicated in some patients. Further, there is much socio-cultural and patient pressure to provide restorations that maintain a "straight, white" appearance of teeth for the patient, regardless of other factors.

The Environmental Impact review found that the risks associated with dental restorative materials are better described for amalgam as opposed to composite resin. For amalgam, the presence of mercury has been of concern for decades. While mercury has been established as a chemical that is persistent, bioaccumulative, and toxic, the relative small contribution of mercury into the Canadian ecosystem from its use in dentistry, as well as the over-time declines in its use, suggest that the potential impacts on the environment are much less than from other sources. There is an increasing use of composite materials as dental fillings, although relatively little is known about most of these chemicals and, in particular, their fate in the environment and downstream impacts on the ecosystem. Most attention and information is on BPA, and while this chemical has been shown to contaminate ecosystems and disrupt fish and wildlife health, linking potential impacts back to the Canadian dental sector is not possible with the current state of knowledge.

The ethics analysis identified a range of issues which can broadly be divided into macro, meso, and micro concerns. Macro-level considerations include ensuring compliance with environmental regulation and directives regarding the appropriate handling of amalgam waste, as well as appropriate funding policies and research to continue to develop quality dental restoration materials. At the meso level, there are questions regarding potential conflicts of interest and financial incentives for selecting one material over another. Additionally, the need for clear communication to patients about the nature of the materials and corresponding benefits or risks was identified. Public health education and clear communication are related to the micro level consideration of informed consent when placing a restoration. Additional micro level considerations include the right for dentists to refuse to provide services they believe to be harmful to patients, and ensuring patients are treated with respect, particularly those who explore possible connections between their restoration material and chronic health issues.

Interpretation

The highest-quality clinical evidence to date has consistently shown dental amalgam to be superior to composite resin in its efficacy (i.e., restoration failure and secondary caries).[6] Furthermore, the most rigorous comparative evidence available indicates that the safety of amalgam and composite resin restorations was comparable in a variety of health outcomes. Our clinical findings corroborate those that have informed the current perspective on dental amalgam use in Canada by Health Canada[19] and the Canadian Dental Association.[219] Similarly, our findings likewise align with, and build upon, the 1997 conclusions generated by the Conseil d'évaluation des technologies de la santé du Québec, which conducted a comprehensive evaluation of the safety of dental amalgam.[220] While their evidence review concluded that there were insufficient data to ascertain the safety, or lack thereof, of dental amalgam to patients, our clinical review of safety found that much of the evidence addressing safety showed no, or very little, difference between amalgam and composite resin, with no discernible pattern of effect.

Likewise, the cost-consequence analysis using time-to-failure favoured amalgam over composite resin as a dental restorative material, based on estimates of lifetime discounted Canadian costs — findings that corroborate those generated by similar studies in the UK[89] and Quebec.[88] Whereas the cost of amalgam separators adds to the cost of providing amalgam restorations, the increased time associated with placing composite resin restorations[90] also introduces increased costs to dental clinics and their practitioners. As the review of implementation issues has shown, these latter cost considerations may impact the decision-making process for choice of restorative material — particularly for dental professionals, as no explicit policy currently dictates their use of amalgam or composite resin material. Importantly, the more frequent failure of composite resin restorations across time and the consequent projected need for crowns and possibly tooth extraction at a younger age is an important consideration for patients in weighing the relative benefits and disadvantages of an amalgam versus a composite resin filling.

Given these evidentiary considerations presented within the current HTA, the controversy described in the ELSI review may at first appear discordant. Nonetheless, as that review has illustrated, values — and the macro, meso, and micro level considerations that underlie them — are informed by facts, yet are also subject to pressure from political, cultural, and other social forces.[153-155] In the case of dental amalgam, the considerable bodies of literature — and rhetoric[221,222] — that have been generated on both sides of the debate present a distinct challenge to the establishment of a truly objective safety profile for dental amalgam. In addition, the relative lack of scientific evidence addressing the potential toxic and environmental harms that composite resin may introduce support the assertion that factors additional to scientific evidence play an important role in the questions surrounding the use of dental materials.

Considering the particularly contentious macro and meso level challenges described, it may be that the micro level clinical interface of dental care provider and patient is where conversations about the benefits and potential harms of various dental materials are best to occur; especially as patient profiles and clinical indications are of particular importance to providers, alongside the significant socio-cultural pressures to maintain a "straight, white" appearance of teeth for the patient, regardless of other factors. And while the available qualitative evidence informing the patient experiences review was limited to those few patients who complain of illness that they perceive was caused by dental amalgam restorations, it remains incumbent upon care providers to listen and hear the concerns of all

patients. In addition, clinicians must remain committed to transparently providing the best available information to support making informed decisions — even when the information is ambiguous or equivocal. Finally, dental care providers should prioritize the provision of opportunities for shared decision-making — if and when the patient so desires — so as to ensure the optimal dental material is made available for a given situation.[223]

Undoubtedly, this ideal of a shared, clinical, decision-making encounter within which to address the best use of dental restorative materials is challenged in the face of perceived questions that persist about the safety of dental restoration materials. This may be exacerbated by the private practice model under which the majority of dentistry operates in Canada, and the various issues identified within our implementation and ELSI reviews that arise within this context. Importantly, questions that linger concerning the efficacy versus the safety of dental amalgam restorations must also be considered in the context of socioeconomic issues; the WHO has highlighted the importance of dental amalgam as a restorative material among those in developing countries, as well as disadvantaged populations in developed nations.[224] This imperative has been echoed in Canada with regard to the use of dental amalgam among disadvantaged Canadians.[225]

Even so, the "changing dynamic" in Canada — as described within our review of implementation issues — may continue to reduce the use of dental amalgam. While Canada has met its obligations, this could be accompanied by pressures associated with the recent ratification of the Minamata Convention.[17] While it remains undisputed that mercury is a chemical that is persistent, bioaccumulative, and toxic, the small contribution from Canadian dentistry suggests that the potential impacts on the environment are much less than from other sources. Despite this, the global political impetus and associated activities intended to phase down and phase out mercury are likely to have important influences on the practise of dentistry and its use of amalgam as a restorative material in the future.[226]

Strengths

The clinical reviews of efficacy and safety limited eligibility criteria to studies comparing dental amalgam with composite resin so as to maximize the scientific rigour underpinning our findings. The 2014 Cochrane SR was deemed to be of high quality using AMSTAR; and Cochrane SRs are considered the gold standard in SRs.[227,228] The update to this review aimed to assess and take guidance from the methods applied to the efficacy outcome from the 2014 Cochrane SR[6] and were likewise rigorous in their search and synthesis of the best available evidence. Because the authors of the 2014 Cochrane SR acknowledged their limited review of adverse effects — particularly citing the need to include observational studies — the review of safety for this HTA included a broad and comprehensive search strategy. Study eligibility was not limited to trial evidence and considered a broad range of study designs, provided they reported on evidence of a direct comparison between dental amalgam and composite resin restorations. And while the measurement of total Hg in urine does not delineate between elemental mercury exposure from dental amalgam restorations as opposed to methylmercury exposure from the consumption of fish,[229] the randomized design informing the studies included in our review of safety provide assurance that this uncertain variable is unlikely to have affected the findings and interpretation. The review methods were conducted and reported in consideration of PRISMA[230] and PRISMA-Harms.[1] Findings from both reviews are based on the results reported from studies with a minimum of three years of follow-up.

Broad literature searches and eligibility criteria were used to inform the economic evaluation, patient perspectives and experiences, environmental, implementation, and ELSI reviews. The economic evaluation contributes a novel cost-consequence model to the Canadian context. The Patients' Perspectives and Experiences Review section of this report sought qualitative studies to inform an in-depth analysis of patients' experiences with amalgam and composite resin restorations. The Implementation Issues section collected information from a variety of sources to identify the most salient barriers and facilitators to the implementation of these interventions in the Canadian context. The environmental review likewise sought a broad base of literature and offers Canadian decision-makers a novel assessment of the contributions of the Canadian dental profession to the burden of mercury contamination — particularly as the Minamata Convention has recently been ratified and its implications are considered. And finally, the ELSI review similarly used broad selection criteria to include a wide range of literature on the issues under investigation. It thus provides a broad historical overview of the persistent questions regarding amalgam safety including reference to the literature on both sides of the debate. (See Appendix 20.)

Limitations

Despite a comprehensive search, available clinical evidence describing direct comparisons of amalgam and composite resin restorations was limited, rendering few eligible studies for our clinical review. Thus, while the decision to focus on comparative studies provided the most compelling evidence describing the relative safety of amalgam versus composite resin restorations, it also resulted in the exclusion of peripherally relevant studies examining the safety of these materials in isolation (e.g., dose-response studies); although these would have provided limited insight into the comparative safety of amalgam and composite resin.

This HTA is constrained by the limitations of the studies we included, including methodological and reporting deficiencies. For instance, the assessment of causality has been identified as an important part of conducting and reporting studies of safety and/or harms.[1] In our review of safety, we found that, while none of the 10 reports from the three included studies described an assessment of causation, one report from the NECAT[38] study and one from the Casa Pia study[41] made reference to causation, stating that the randomized design allowed for causal inference of psychosocial outcomes[38] and renal function,[41] respectively. Another report generated from the NECAT study[40] explicitly stated that amalgam was found to not be a cause of immune deficiency, but likewise failed to describe any formal or other assessment of causality. And lastly, another report from the NECAT[42]study briefly mentioned a possible causal association between amalgam exposure and microalbuminuria in its discussion but, again, did not describe a formal assessment of causality, and offers another explanation — i.e., that its finding may be due to chance. The remaining papers included in our review of safety make no explicit mention of causation.[37-39,43,44]

The comparison of materials as different in composition as amalgam and composite resin is challenging for a number of reasons including their relative differences in composition across time (i.e., whereas amalgam has remained virtually the same in its composition, composite resin has, and is, changing in stride with research and development). Studies included in both the Cochrane SR's analysis of efficacy and our review of safety (i.e., the NECAT and Casa Pia studies) were initiated in the late 1990s, possibly rendering the composite resin materials used at that time obsolete compared with those in use today. Extending from this, the integration of studies across time may be misleading because of advances in dental techniques, tools, and materials.

Studies included in both of the reviews did not explicitly or consistently report data on restoration size, which limited the interpretation of the findings for this variable. Our investigation of efficacy sought teeth as the unit of interest, which necessarily did not allow for consideration of individual-level variables (e.g., individual physiological wear, masticatory equilibrium, caries risk, abrasion, attrition, etc.), which are known to vary based on individual characteristics.[32,231] Likewise, the studies included in our review of safety did not report any explicit, quantitative findings, as it concerned potential risk factors for exposure related to such individual-level variables like mastication, gum-chewing, or pH. Included reports from the NECAT study described a higher prevalence of caries in study participants as compared with that in the population, which was associated with eligibility criterion of at least two carious lesions at baseline.[38,45] As well, because participants in the NECAT study were not genotyped, genetic susceptibility could not be investigated.[40] Authors of the NECAT study also conceded that no biomarker data on monomers were collected in children receiving composite resin restorations, limiting the extent to which toxicity from dental composite materials could be interpreted.[37] As it concerned the investigation of neuropsychological effects, children with related, pre-existing conditions were excluded from the trial; consequently, investigators were unable to ascertain whether — or to what extent — either amalgam and/or composite resin restorations may exacerbate such conditions.[45] Furthermore, most findings from both reviews were reported in children, allowing for limited generalizeability to the wider population.

Studies were sufficiently heterogeneous in their methods and measures, as well as deemed to be at a high or unclear risk of bias for multiple domains of the Cochrane Risk of Bias Tool, such that meta-analyses could not be undertaken. For instance, the amalgam restorations used in the study identified as part of the 2014 Cochrane SR update were bonded,[36] making their features different from those evaluated in the NECAT and Casa Pia studies reported within the primary analyses of the 2014 Cochrane SR.[6] The length of follow-up in all included studies may have been insufficient to adequately evaluate the outcomes under investigation; in particular, three years may not be sufficient follow-up for identifying and differentiating the degree to which efficacy varied between dental materials.[232] And importantly, the clinical significance of some statistically significant differences between treatment groups was not always clear (e.g., differences in urinary mercury levels and post-operative pain scores, for instance). Finally, authors of included studies were not contacted for additional information and/or where clarity was needed.

As with all economic analyses, the results were limited by both the quality and quantity of data available to inform model inputs. We were faced with a significant lack of data for this analysis and this represents a major limitation. We did not have access to patient-level data from the NECAT study and thus were limited to the published evidence from that study. This forced us to digitalize the published survival curves and hence might have increased uncertainty. Furthermore, it limited our possibilities in terms of modelling (e.g., failure rate according to type of tooth or number of surfaces restored, etc.). We were not able to find enough information on the natural history following a failed tooth restoration and had to make assumptions that significantly limit the face validity of the results. Although our set of dental fees from the public programs is almost complete, the one for privately funded services was limited; in particular we were not able to obtain suggested fees from the two largest provinces (i.e., Ontario and Quebec). Furthermore, we were not able to find a good source of information on the procedure time for composite resin restorations and had to base the analysis on feedback from the clinical experts consulted in this review. Despite these limitations, this analysis represents a first estimation, using the best evidence available, of the costs and consequences of using amalgam and composite resin for

restoration of permanent posterior teeth, and the findings overall remained robust to most sensitivity analyses.

Although the research question for the patient experiences review sought experiences related to both amalgam and composite resin, the limited eligible qualitative evidence described only negative experiences with amalgam, indicating that some patients have perceived illness from amalgam fillings. Importantly, quantitative studies in this area have suggested that patients with these experiences represent a very small minority[233,234] and often have additional health concerns as compared to those within the general population — even following the removal of amalgam fillings.[235,236] This highlights an additional limitation; i.e., the cause of ailments in patients informing the findings of the studies included in our review was unknown. Thus, the appropriateness of a diagnosis of mercury poisoning cannot be ascertained. We therefore do not know if the chosen strategy of amalgam replacement would have any effect on the patients' health. Further, we are missing the experiences of children, adolescents, and the elderly — and, importantly for this HTA, the experiences of Canadian dental patients. This may be a particularly important limitation, as removal of amalgam fillings and detoxification are not recommended by the Canadian Dental Association and so the findings of the studies included in this section of the HTA may lack any transferability to the Canadian context. In addition, there are other outcomes that speak to the experiences of patients with dental restorations — such as deterioration of the restoration and the length of time for repair, or if new restorations are needed, or the length of time to the loss of the tooth. Finally, the patient preference for "white fillings" identified in the review of implementation issues was not addressed by any of the studies identified by the patient experiences review, suggesting an important gap in the qualitative evidence base addressing patient experiences with these dental materials.

For the implementation issues literature review, Canadian studies only were searched for and included. Because of this restriction, studies that may be relevant to the Canadian context but were not authored in Canada were therefore missing from the analysis. Additionally, only one reviewer extracted and analyzed the data from the literature. One of the limitations of having a single reviewer is that there is no opportunity for discussion of the literature, or the potential for challenges to the initial analyses. More than half of the relevant literature articles were greater than five-years-old and mostly focused on patient factors and the education of providers. Additionally, although all of the studies had information on the Canadian context, six of the studies were specifically Canadian only. In the consultations, some of the limitations were the small stakeholder sample size, which was not randomly-recruited, and the lack of representation from private practitioners or patients.

The main limitation of the Environmental Impact review was similarly a dearth of available, relevant information. While there are several studies to draw from for estimates concerning mercury use and its release from amalgams, in many cases the estimates are outdated, may not accurately reflect the current situation, and are likely overestimates given the continuing decreasing trend toward the use of amalgam. For composite resins, there are no strong or relevant data sets available, and thus it is not possible to perform any meaningful calculations to characterize the environmental source, fate, exposure, and hazards associated with these materials.

Directions for Future Research

Given the limitations and risk of bias in much of the body of evidence addressing potential toxicity from amalgam and/or composite resin restorations, there remains a need for methodologically rigorous studies that focus on broader populations and pursue longer-term follow-up than those included in our clinical review of the evidence. For example, considering the finding from the Casa Pia trial that no statistically significant difference was found in unadjusted urinary mercury levels at seven years' follow-up (whereas a significant group difference was found at all other time points in the unadjusted analyses), a longer term of follow-up may be able to illuminate any potential reduction (or not) in exposure over time. In addition, given the concerns identified around genetic susceptibility to materials used in dental restorations — either amalgam or composite resin[237-239] — rigorous, comparative, and controlled clinical research in this area may be further warranted. Importantly, research among disadvantaged and vulnerable populations will be critical, as it concerns issues of access and cost.[224,225,240]

Likewise, the current economic analysis highlights the need for better-quality evidence. As dental claims to both private insurance and public programs in Canada require reporting at the patient's tooth level (e.g., tooth number, surface repaired, time since last restoration), these programs represent an untapped source of evidence. These databases could be used to perform comparative effectiveness studies (e.g., amalgam versus composite resin restorations, comparison of different clinical pathways) and epidemiological studies (e.g., natural history of tooth restorations, prevalence studies, etc.) that can help better support the modelling of long-term outcomes. Such retrospective observational studies using administrative databases, despite their limitations, have been performed in Canada[241] and in other jurisdictions.[73,242] As dental fee codes are the same throughout Canada, except for one province, it might also be possible to combine these databases of patient-level data all into a single Canadian database for broad Canadian population analyses. Whereas important limitations exist as they concern the types of data available within these repositories, such population-based analyses would provide up-to-date evidence in a real-life setting that could help to inform dental health policy-making or guide future research.

Given the significant gaps in the qualitative evidence base, the experiences of patients with composite resins — as well as those with amalgam restorations who are not selected based on their complaints associated with said restorations — will be important; as will be an increase of the age range of participants to provide the perspectives of children, adolescents, and the elderly. Future research efforts might also focus on the barriers and facilitators of implementing both restorative materials in private practice. Additionally, areas of the INTEGRATE-HTA framework that were not well-represented by the literature or consultations in this report could also be explored in future.

Concerning the impact of dental materials on the environment, it would be useful to better characterize the contemporary use of mercury within the dental sector so that relevant estimates of environmental risk may be generated. This would also aid in Canada's commitment to the Minamata Convention. Concerning composite resins, there is a significant need for detailed research on the matter covering all aspects of their potential environmental risk across the entire life cycle. There is also a need to understand the use practices of various composite materials across the Canadian dental sector. Following use within the clinic, there is likewise a need to understand their potential releases of materials (and chemicals) across their entire life cycle into ecosystems and ultimately their fate and behaviour in various media. Next, there is a need to better understand potential exposure by

biota to various materials (and chemicals) and whether such exposures are associated with adverse health outcomes.

Given the persistent questions surrounding amalgam and the remaining uncertainties around the health and environmental effects of BPA and other compounds in composite resin, investments in innovation and development are also an important consideration. Despite the long-term investment and costs, dental materials that can demonstrably offer improved efficacy and safety over those currently used in contemporary dentistry may be warranted.[224,243]

Conclusions

The best available evidence indicates that, compared with composite resin, amalgam restorations appear to be more clinically efficacious and as safe, while also costing less. In addition, dental amalgam waste constitutes a small relative contribution to overall mercury contamination in the Canadian environment compared with other sources — largely owing to the judicious management of resultant mercury waste.

Although there is a global effort to phase down the use of dental amalgam, and because composite resin materials undergo continual development and improvement, the findings of this HTA suggest limited rationale to discontinue the use of dental amalgam in Canada.

At the individual dental practice level, providers may choose to offer patients only one type of material for a number of reasons; among those who choose to provide both, however, there is a real opportunity for them to engage in discussion and shared decision-making with patients to balance the desirable and undesirable consequences of using either type of restorative material.

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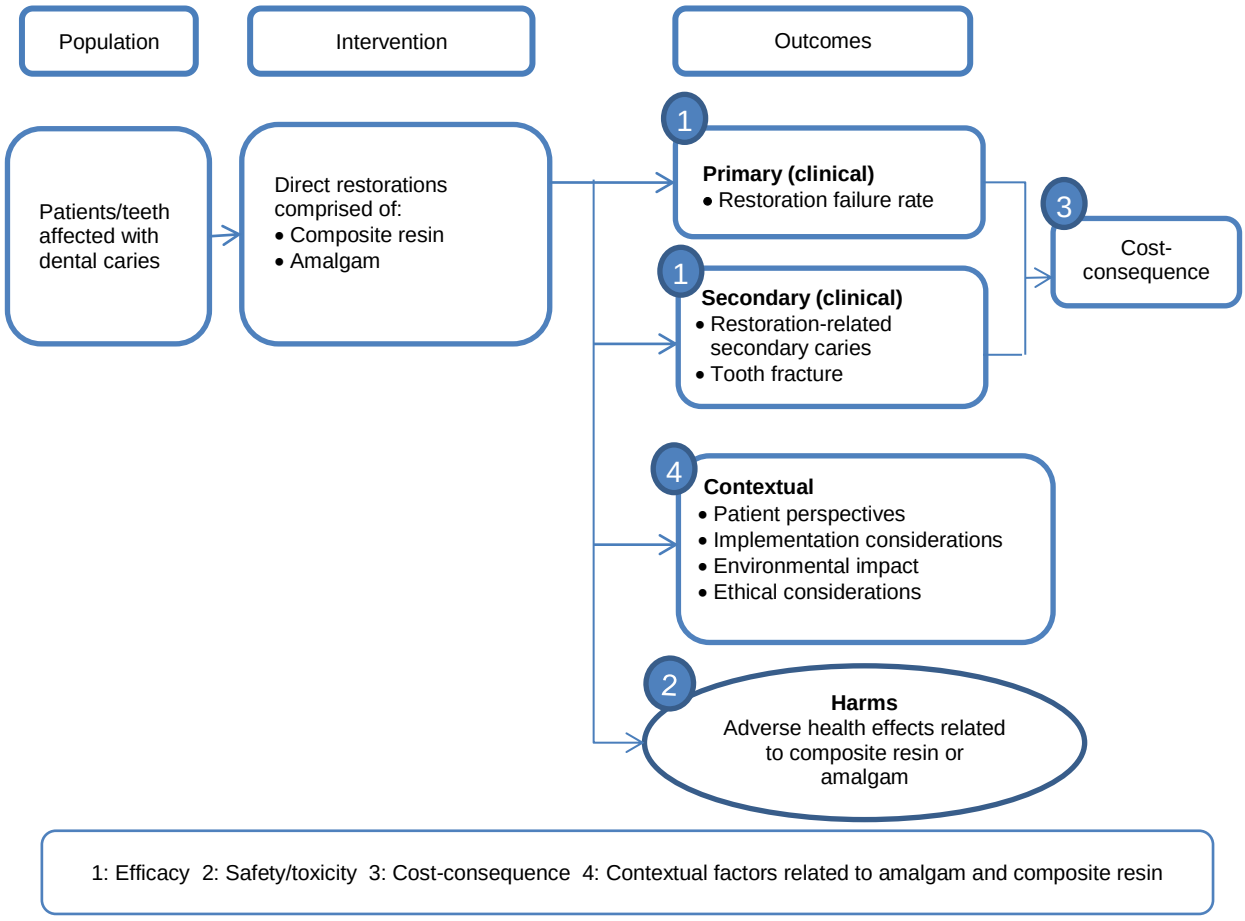
Appendix 1: Analytical Framework



Appendix 2: Literature Search Strategy

Clinical Review Database Search

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials May 2017 Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to Present MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 26, 2017
Alerts:	Monthly search updates were run until February 1, 2018
Search filters:	Clinical effectiveness search: no filters were applied Safety search: safety filters
Limits:	Date limits: • Clinical effectiveness search: 2012 – present • Safety search: none for dental amalgam search; 2006-present for composite resin search Language limits: • none applied Conference abstracts: • Clinical effectiveness search: included • Safety search: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
$	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings Requires words are adjacent to each other (in any order)
adj adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf .af	Author keyword heading word (MEDLINE) All fields (Cochrane Central)
.kw	Author keyword (Embase); keyword (Cochrane Central)
.jw .jx .pt	Journal word (MEDLINE) Journal word (Embase) Publication type
/ae	Subject heading qualifier (MEDLINE); adverse effects Subject heading qualifier (Embase); adverse drug reaction

SYNTAX GUIDE	
/tu	Subject heading qualifier (MEDLINE); therapeutic use
/th	Subject heading qualifier; therapy
/ct	Subject heading qualifier (MEDLINE); contraindications
/po	Subject heading qualifier (MEDLINE); poisoning
/to	Subject heading qualifier (MEDLINE); toxicity Subject heading qualifier (Embase); drug toxicity
/bl	Subject heading qualifier (MEDLINE); blood
/mo	Subject heading qualifier (MEDLINE); mortality
/co	Subject heading qualifier (MEDLINE); complications
/am	Subject heading qualifier (Embase); adverse device effect
ppez	Ovid database code: MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code: Embase 1974 to present, updated daily
cctr	Ovid database code: Cochrane Central Register of Controlled Trials

Research Question 1: Clinical Efficacy

#	MULTI-DATABASE SEARCH STRATEGY
1	exp Dental restoration, permanent/
2	Dental restoration, temporary/
3	((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).ti,ab,kf.
4	or/1-3
5	Dental amalgam/
6	amalgam$.ti,ab,kf.
7	or/5-6
8	exp Composite resins/
9	((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab,kf.
10	(enamel bond$ or (concise adj3 resin$) or (white adj3 sealant$) or conclude resin$ or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Silux).ti,ab,kf.
11	or/8-10
12	4 and 7 and 11
13	12 use ppez
14	exp Dental Restoration, Permanent/
15	exp Dental Restoration, Temporary/
16	((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).af.
17	or/14-16
18	Dental amalgam/
19	amalgam$.ti,ab,kw.
20	or/18-19
21	exp Composite resins/
22	((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab,kw.
23	(enamel bond$ or (concise adj3 resin$) or (white adj3 sealant$) or conclude resin$ or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Keywords or Silux).ti,ab,kw.
24	or/21-23
25	17 and 20 and 24
26	25 use cctr
27	Tooth filling/
28	((tooth or teeth or molar$ or bicuspid$ or "Class I" or "Class II") and (restor$ or fill$)).ti,ab,kw.
29	or/27-28
30	exp Dental alloy/
31	amalgam$.ti,ab,kw.
32	or/30-31
33	exp Resin/

#	MULTI-DATABASE SEARCH STRATEGY
34	((resin$ adj3 composite$) or "bisphenol A-Glycidyl methacrylate" or compomer$ or Bis-GMA).ti,ab,kw.
35	(enamel bond$ or (concise adj3 resin$) or (white adj3 sealant$) or conclude resin$ or Adaptic or Delton or Epoxylite-9075 or (Kerr adj5 seal$) or Nuva-seal or Panavia or Retroplast or Silux).ti,ab,kw.
36	or/33-35
37	29 and 32 and 36
38	37 use oemezd
39	13 or 26 or 38
40	limit 39 to yr="2012 -Current"
41	remove duplicates from 40

Research Question 2: Safety

#	MULTI-DATABASE SEARCH STRATEGY
1	Dental amalgam/
2	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and (Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kf,kw.)
3	((silver or mercury) and (dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*)).ti,ab,kf,kw.
4	(amalgam or amalgams).ti,ab,kf,kw. and (Silver/ or Mercury/ or (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kf,kw.)
5	(amalgam or amalgams).ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
6	or/1-5
7	6 use ppez
8	6 use cctr
9	Dental amalgam/
10	Dental alloy/ and Amalgam/
11	(Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th) and (Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kw.)
12	((silver or mercury) and (dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*)).ti,ab,kw.
13	(amalgam/ or (amalgam or amalgams).ti,ab,kw.) and (Silver/ or Mercury/ or (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kw.)
14	(amalgam or amalgams).ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jx.
15	or/9-14
16	15 use oemezd
17	conference abstract.pt.
18	16 not 17
19	7 or 8 or 18
20	exp safety/
21	equipment safety/
22	exp equipment failure/
23	consumer product safety/
24	"product recalls and withdrawals"/
25	medical device recalls/
26	"safety-based medical device withdrawals"/
27	product surveillance, postmarketing/
28	postmarketing surveillance/
29	clinical trial, phase iv.pt.
30	phase 4 clinical trial/
31	clinical trials, phase iv as topic/
32	"phase 4 clinical trial (topic)"/
33	exp postoperative complications/

#	MULTI-DATABASE SEARCH STRATEGY
34	exp postoperative complication/
35	exp intraoperative complications/
36	peroperative complication/
37	exp side effect/
38	"side effects (treatment)"/
39	exp adverse drug reaction/
40	exp drug safety/
41	exp "drug toxicity and intoxication"/
42	exp "drug-related side effects and adverse reactions"/
43	exp drug-induced liver injury/
44	exp drug hypersensitivity/
45	drug recalls/
46	drug recall/
47	safety-based drug withdrawals/
48	abnormalities, drug-induced/
49	exp "side effects (drug)"/
50	(hazard* or defect* or misuse* or failure* or malfunction* or error*).ti,kf,kw.
51	(safe* or adverse* or undesirable or harm* or injurious or risk or risks or reaction* or complication* or poison*).ti,kf,kw.
52	(side effect* or safety or unsafe).ti,ab,kf,kw.
53	((adverse or undesirable or harm* or toxic or injurious or serious or fatal) adj3 (effect* or reaction* or event* or outcome* or incident*)).ab.
54	((drug or chemically) adj induced).ti,ab,kf,kw.
55	(toxic or toxicit* or toxologic* or intoxication or noxious or tolerability or teratogen*).ti,ab,kf,kw.
56	(warning* or recall* or withdrawn* or withdrawal*).ti,kf,kw.
57	(death or deaths or fatal or fatality or fatalities).ti,kf,kw.
58	exp environmental exposure/
59	or/20-58
60	19 and 59
61	Dental amalgam/ae, ct, po, to
62	exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/ or exp Dental caries/th or Dental amalgam/ or (amalgam or amalgams or dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kf,kw.
63	Silver/ae, ct, to or Mercury/ae, to, bl or exp Mercury poisoning/ or exp Mercury poisoning, nervous system/
64	62 and 63
65	exp Dental Restoration, Permanent/ae, ct, mo or Dental Restoration, Temporary/ae, ct or Dental Materials/ae, co, ct, po, to
66	Dental amalgam/ or Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kf,kw.
67	65 and 66
68	61 or 64 or 67
69	68 use ppez
70	68 use cctr
71	Dental amalgam/ae, to
72	Dental alloy/ae, to and amalgam/am, ae, to
73	Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th or Dental alloy/ or dental amalgam/ or (amalgam or amalgams or dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kw.
74	Silver/ae, to or Mercury/ae, to or Mercurialism/
75	73 and 74
76	amalgam/am, ae, to and (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kw.
77	Dental procedure/ae or Dental Material/am, ae, to
78	Amalgam/ or Dental amalgam/ or (amalgam or amalgams or silver or mercury).ti,ab,kw.
79	77 and 78
80	71 or 72 or 75 or 76 or 79
81	80 use oemezd
82	81 not 17

#	MULTI-DATABASE SEARCH STRATEGY
83	69 or 70 or 82
84	60 or 83
85	exp Composite Resins/
86	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and composite*.ti,ab,kf,kw.
87	(composite* adj3 (resin* or restor* or filling* or dental or dentist* or conventional or microfilled or macrofilled or hybrid or flowable or packable or nanofilled or direct or indirect or small particle* or condensable or bonded or non-bonded or nonbonded)).ti,ab,kf,kw.
88	(composite* adj3 (poly-acid or polyacid or polyacrylate or polyacrylic or acrylic)).ti,ab,kf,kw.
89	((resin or resins) adj3 (filled or unfilled or synthetic* or dental or restor*)).ti,ab,kf,kw.
90	((tooth-colored or tooth-coloured) adj3 (filling* or restor*)).ti,ab,kf,kw.
91	(White adj3 filling*).ti,ab,kf,kw.
92	exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th or (composite* or resin or resins).ti,ab,kf,kw.
93	Bisphenol A-Glycidyl Methacrylate/ or (alumino silicate polyacrylic acid or "bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA or triethylene glycol dimethacrylate or urethane dimethacrylate*).ti,ab,kf,kw.
94	92 and 93
95	Compomer*.ti,ab,kf,kw.
96	composite*.ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
97	or/85-91,94-96
98	97 use ppez
99	97 use cctr
100	exp Resin/ and composit*.ti,ab,kw.
101	(Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th) and composite*.ti,ab,kw.
102	(composite* adj3 (resin* or restor* or filling* or dental or dentist* or conventional or microfilled or macrofilled or hybrid or flowable or packable or nanofilled or direct or indirect or small particle* or condensable or bonded or non-bonded or nonbonded)).ti,ab,kw.
103	(composite* adj3 (poly-acid or polyacid or polyacrylate or polyacrylic or acrylic)).ti,ab,kw.
104	((resin or resins) adj3 (filled or unfilled or synthetic* or dental or restor*)).ti,ab,kw.
105	((Tooth-colored or tooth-coloured) adj3 (filling* or restor*)).ti,ab,kw.
106	(White adj3 filling*).ti,ab,kw.
107	Dental restoration/ or Dental Material/ or Tooth Filling/ or exp Dental Caries/th or (composite* or resin or resins).ti,ab,kw.
108	"bisphenol A bis(2 hydroxypropyl) ether dimethacrylate"/ or (alumino silicate polyacrylic acid or "bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA or triethylene glycol dimethacrylate or urethane dimethacrylate*).ti,ab,kw.
109	107 and 108
110	Compomer*.ti,ab,kw.
111	composite*.ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jx.
112	or/100-106,109-111
113	112 use oemezd
114	113 not 17
115	98 or 99 or 114
116	59 and 115
117	exp Composite Resins/ae, ct, to
118	exp Dental Restoration, Permanent/ae, ct, mo or Dental Restoration, Temporary/ae, ct or Dental Materials/ae, co, ct, po, to
119	Composite resins/ or (composite* or resin or resins).ti,ab,kf,kw.
120	118 and 119
121	exp Dental Restoration, Permanent/ae, ct, mo or Dental Restoration, Temporary/ae, ct or Dental Materials/ae, co, ct, po, to
122	("bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA).ti,ab,kf,kw.
123	121 and 122
124	117 or 120 or 123
125	124 use ppez
126	124 use cctr

#	MULTI-DATABASE SEARCH STRATEGY
127	exp Resin/am, ae, to and composit*.ti,ab,kw.
128	Dental procedure/ae or Dental Material/am, ae, to
129	exp Resin/ or (composite* or resin or resins).ti,ab,kw.
130	128 and 129
131	Dental procedure/ae or Dental Material/am, ae, to
132	("bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA).ti,ab,kw.
133	131 and 132
134	127 or 130 or 133
135	134 use oemezd
136	135 not 17
137	125 or 126 or 136
138	116 or 137
139	limit 138 to yr="2006 -Current"
140	84 or 139
141	limit 140 to yr="2005 -Current"
142	140 not 141
143	remove duplicates from 141
144	remove duplicates from 142
145	143 or 144
146	from 145 keep 1-3870
147	from 145 keep 3871-5871

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Library	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used	
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.	
Scopus	Searched to capture records not indexed in MEDLINE. Keyword search and limits based on MEDLINE search, with appropriate syntax used.	
Cochrane Oral Health Group's Trials Register	Searched to capture records not indexed in MEDLINE. Same keywords used as per MEDLINE search. Syntax adjusted for Cochrane Oral Health Group's Trials Register. *(Database not publically available; search completed by the Information Specialist at the Cochrane Oral Health group)*	
LILACs	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords, and date limits used as per MEDLINE search. Syntax adjusted for LILACs database. *(LILACs search completed only for Q1 clinical efficacy)*	

Patient Perspectives and Experiences Database Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE Daily and MEDLINE 1946 to Present MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations
Date of Search:	Qualitative studies search: June 8, 2017 Patient preferences search: July 20, 2017
Alerts:	Monthly search updates were run until February 1, 2018
Search filters:	Qualitative studies; patient preferences
Limits:	Date limit: none Language limit: none

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings Truncation symbol for one or no characters only
?	Before a word, indicates that the marked subject heading is a primary topic;
$	or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word
.jw	Journal title word
.jn	Journal name
freq=2	Frequency (must appear at least two times)
/tu	Subject heading qualifier: therapeutic use
/th	Subject heading qualifier: therapy
ppez	Ovid database code: MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present

Qualitative Studies Database Search

#	DATABASE SEARCH STRATEGY
1	Dental amalgam/
2	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and (Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kf.)
3	((silver or mercury) and (dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*)).ti,ab,kf.
4	(amalgam or amalgams).ti,ab,kf. and (Silver/ or Mercury/ or (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kf.)
5	(amalgam or amalgams).ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
6	or/1-5
7	exp Composite Resins/
8	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and composite*.ti,ab,kf.
9	(composite* adj3 (resin* or restor* or filling* or dental or dentist* or conventional or microfilled or macrofilled or hybrid or flowable or packable or nanofilled or direct or indirect or small particle* or condensable or bonded or non-bonded or nonbonded)).ti,ab,kf.
10	(composite* adj3 (poly-acid or polyacid or polyacrylate or polyacrylic or acrylic)).ti,ab,kf.
11	((resin or resins) adj3 (filled or unfilled or synthetic* or dental or restor*)).ti,ab,kf.
12	((tooth-colored or tooth-coloured) adj3 (filling* or restor*)).ti,ab,kf.
13	(White adj3 filling*).ti,ab,kf.
14	exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th or (composite* or resin or resins).ti,ab,kf.
15	Bisphenol A-Glycidyl Methacrylate/ or (alumino silicate polyacrylic acid or "bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA or triethylene glycol dimethacrylate or urethane dimethacrylate*).ti,ab,kf.
16	14 and 15
17	Compomer*.ti,ab,kf.
18	composite*.ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
19	7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17 or 18

#	DATABASE SEARCH STRATEGY
20	6 or 19
21	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or Narration/ or Nursing Methodology Research/
22	Interview/
23	interview*.ti,ab,kf.
24	qualitative.ti,ab,kf,jn.
25	(theme* or thematic).ti,ab,kf.
26	ethnological research.ti,ab,kf.
27	ethnograph*.ti,ab,kf.
28	ethnonursing.ti,ab,kf.
29	phenomenol*.ti,ab,kf.
30	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
31	(life stor* or women* stor*).ti,ab,kf.
32	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
33	(data adj1 saturat$).ti,ab,kf.
34	participant observ*.ti,ab,kf.
35	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
36	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
37	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
38	(field adj (study or studies or research)).ti,ab,kf.
39	human science.ti,ab,kf.
40	biographical method.ti,ab,kf.
41	theoretical sampl*.ti,ab,kf.
42	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
43	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
44	(life world or life-world or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
45	((lived or life) adj experience*).ti,ab,kf.
46	cluster sampl*.ti,ab,kf.
47	observational method*.ti,ab,kf.
48	content analysis.ti,ab,kf.
49	(constant adj (comparative or comparison)).ti,ab,kf.
50	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
51	narrative analys?s.ti,ab,kf.
52	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
53	(van adj manen*).ti,ab,kf.
54	(van adj kaam*).ti,ab,kf.
55	((corbin* adj2 strauss*) or mixed method*).ti,ab,kf.
56	or/21-55
57	20 and 56

Patient Perspectives Database Search

#	DATABASE SEARCH STRATEGY
1	Dental amalgam/
2	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and (Silver/ or Mercury/ or (amalgam or amalgams or silver or mercury).ti,ab,kf.)
3	((silver or mercury) and (dental or dentist* or tooth or teeth or filling* or premolar* or molar* or bicuspid* or incisor* or cuspid*)).ti,ab,kf.
4	(amalgam or amalgams).ti,ab,kf,kw. and (Silver/ or Mercury/ or (dental or dentist* or tooth or teeth or silver or mercury or filling* or restor* or premolar* or molar* or bicuspid* or incisor* or cuspid*).ti,ab,kf.)
5	(amalgam or amalgams).ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
6	or/1-5

#	DATABASE SEARCH STRATEGY
7	exp Composite Resins/
8	(exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th) and composite*.ti,ab,kf.
9	(composite* adj3 (resin* or restor* or filling* or dental or dentist* or conventional or microfilled or macrofilled or hybrid or flowable or packable or nanofilled or direct or indirect or small particle* or condensable or bonded or non-bonded or nonbonded)).ti,ab,kf.
10	(composite* adj3 (poly-acid or polyacid or polyacrylate or polyacrylic or acrylic)).ti,ab,kf.
11	((resin or resins) adj3 (filled or unfilled or synthetic* or dental or restor*)).ti,ab,kf.
12	((tooth-colored or tooth-coloured) adj3 (filling* or restor*)).ti,ab,kf.
13	(White adj3 filling*).ti,ab,kf.
14	exp Dental Restoration, Permanent/ or Dental Restoration, Temporary/ or Dental Materials/tu or exp Dental caries/th or (composite* or resin or resins).ti,ab,kf.
15	Bisphenol A-Glycidyl Methacrylate/ or (alumino silicate polyacrylic acid or "bisphenol A-Glycidyl methacrylate" or Bis-GMA or BisGMA or triethylene glycol dimethacrylate or urethane dimethacrylate*).ti,ab,kf.
16	14 and 15
17	Compomer*.ti,ab,kf.
18	composite*.ti. and (dentist* or dental or oral biology or oral bioscience* or oral health or oral research or endodont* or oral science or caries research or oral medical or dentaire or stomatolog*).jw.
19	or/7-13,16-18
20	6 or 19
21	exp patient acceptance of health care/ or caregivers/
22	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or questionnaire* or Likert or barrier* or facilitator*)).ti.
23	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or questionnaire* or Likert or barrier* or facilitator*)).ab,kf.
24	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or questionnaire* or Likert or barrier* or facilitator*)).ab. /freq=2
25	((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or

#	DATABASE SEARCH STRATEGY
	nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or interview* or questionnaire* or Likert or barrier* or facilitator*)).ab. /freq=2
26	(patient adj (reported or centered* or centred* or focused)).ti,ab,kf.
27	(treatment* adj2 (satisf* or refus*)).ti,ab,kf.
28	(lived experience* or shared decision making).ti,ab,kf.
29	or/21-28
30	20 and 29

OTHER DATABASES	
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.
Scopus	Searched to capture records not indexed in MEDLINE. Keyword search and limits based on MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	July 2017
Keywords:	Dental amalgam, composite resin
Limits:	Date limit: for guidelines only: 2000-present Language limit: none

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for searching health-related grey literature” (https://www.cadth.ca/grey-matters) will be searched:

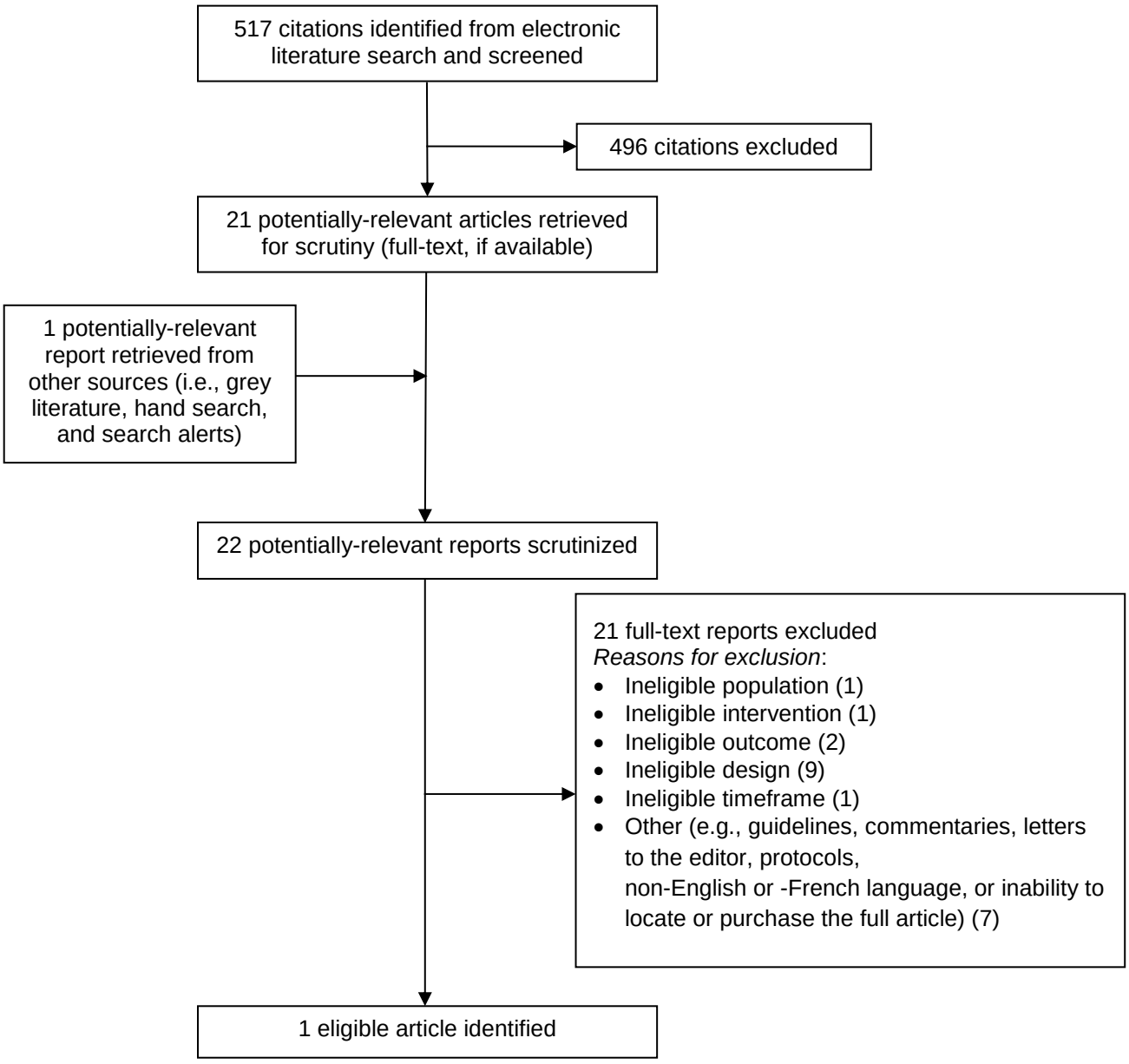
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals

Appendix 3: Process and Method for Systematic Review Update — Clinical Review (Question 1)

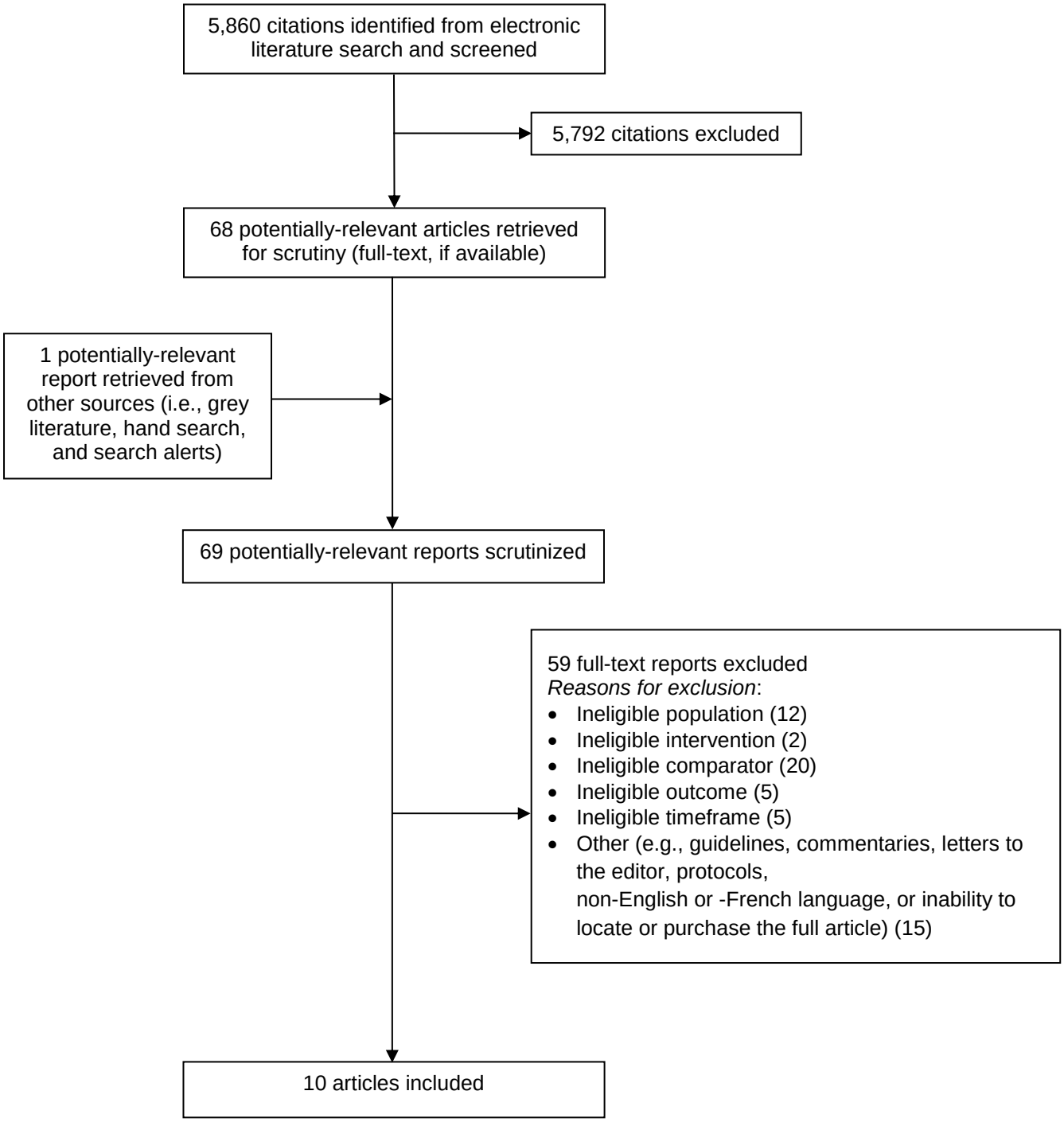
Decision	Approach	Rationale(s)
Limit the update to the efficacy outcome from the 2014 Cochrane SR for the HTA clinical review, Question 1	Methods from the 2014 Cochrane SR were broadly adhered to, but limited to the assessment of efficacy and modified (as below). A de novo systematic review was conducted for safety.	While the original SR's assessment of efficacy was aligned with the HTA's protocol, its assessment of safety was limited
Redfine the population of interest	The population of interest was redefined (i.e., permanent, posterior teeth with dental caries) in order to align with the unit of analysis	Authors of the original review reported issues with the unit of analysis i.e., restoration,[6] whereas the population of interest was people with permanent, posterior teeth
Search strategy was modified	Additional field codes were added, in consultation with the original information specialists from the 2014 Cochrane SR, as follows: • Cochrane Central -.af (all fields) • MEDLINE -.kf (author keyword heading word) • Embase -.kw (author keyword) Subject headings were exploded, as follows: • Dental restoration, permanent (in MEDLINE) Dental alloy (in Embase)	To improve upon the search retrieval from the original 2013 search strategy, minor modifications were made
Study screening process was modified	As opposed to independent review of each title and abstract by two reviewers, all titles and abstracts deemed potentially eligible by either reviewer were screened at the full-text phase	This conservative approach that was adopted represented a minor methodological deviation from that taken in the 2014 Cochrane SR and posed no threat to overlooking eligible studies, as studies deemed by any one reviewer to be potentially eligible would then be reviewed in full
Method for data abstraction was modified	As opposed to duplicate data abstraction by two independent reviewers, data were abstracted by one reviewer and validated by a second reviewer	A minor methodological deviation from that taken in the 2014 Cochrane SR was implemented to improve efficiency, and was deemed to pose no threat to data integrity
Quality assessment of body of evidence was not performed	No assessment of the quality of body of evidence was conducted	GRADE was deemed to be outside the scope of the HTA's objectives

Appendix 4: Study Selection Flow Diagrams — Clinical Reviews

Research Question 1



Research Question 2



Appendix 5: List of Included Studies — Clinical Review

Research Question 1

Kemaloglu H, Pamir T, Tezel H. A 3-year randomized clinical trial evaluating two different bonded posterior restorations: amalgam versus resin composite. Eur J Dent. 2016 Jan;10(1):16-22.

Research Question 2

Kemaloglu H, Pamir T, Tezel H. A 3-year randomized clinical trial evaluating two different bonded posterior restorations: amalgam versus resin composite. Eur J Dent. 2016 Jan;10(1):16-22.

Maserejian NN, Hauser R, Tavares M, Trachtenberg FL, Shrader P, McKinlay S. Dental composites and amalgam and physical development in children. J Dent Res. 2012 Nov;91(11):1019-25.

Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, McKinlay S. Dental amalgam and psychosocial status: the New England Children's Amalgam Trial. J Dent Res. 2008 May;87(5):470-4.

Woods JS, Martin MD, Leroux BG, DeRouen TA, Bernardo MF, Luis HS, et al. Urinary porphyrin excretion in children with mercury amalgam treatment: findings from the Casa Pia Children's Dental Amalgam Trial. J Toxicol Environ Health A. 2009;72(14):891-6.

Shenker BJ, Maserejian NN, Zhang A, McKinlay S. Immune function effects of dental amalgam in children: a randomized clinical trial. J Am Dent Assoc. 2008 Nov;139(11):1496-505.

Woods JS, Martin MD, Leroux BG, DeRouen TA, Bernardo MF, Luis HS, et al. Biomarkers of kidney integrity in children and adolescents with dental amalgam mercury exposure: findings from the Casa Pia children's amalgam trial. Environ Res. 2008 Nov;108(3):393-9.

Barregard L, Trachtenberg F, McKinlay S. Renal effects of dental amalgam in children: the New England Children's Amalgam Trial. Environ Health Perspect. 2008 Mar;116(3):394-9.

Lauterbach M, Martins IP, Castro-Caldas A, Bernardo M, Luis H, Amaral H, et al. Neurological outcomes in children with and without amalgam-related mercury exposure: seven years of longitudinal observations in a randomized trial. J Am Dent Assoc. 2008 Feb;139(2):138-45.

Woods JS, Martin MD, Leroux BG, DeRouen TA, Leitao JG, Bernardo MF, et al. The contribution of dental amalgam to urinary mercury excretion in children. Environ Health 3901 Perspect. 2007 Oct;115(10):1527-31.

Bellinger DC, Daniel D, Trachtenberg F, Tavares M, McKinlay S. Dental amalgam restorations and children's neuropsychological function: the New England Children's Amalgam Trial. Environ Health Perspect. 2007 Mar;115(3):440-6.

Appendix 6: List of Excluded Studies and Reasons for Exclusion — Clinical Review

Research Question 1

Reference	Reason for Exclusion
Rodríguez-Farre E, Testai E, Bruzell E, De JW, Schmalz G, Thomsen M, et al. The safety of dental amalgam and alternative dental restoration materials for patients and users. Regul Toxicol Pharmacol. 2016 Aug;79:108-9.	Ineligible design i.e., not an RCT
Kreulen CM, Gerritsen AE, Creugers NH. Resin composite restorations for the elderly patient. Gerodontology. 2014 Dec;31(4):243-4.	Ineligible publication i.e., commentary
Lynch CD, McConnell RJ, Wilson NH. Posterior composites: the future for restoring posterior teeth? Prim Dent J. 2014 May;3(2):49-53.	Ineligible publication i.e., commentary
van de Sande FH, Opdam NJ, Truin GJ, Bronkhorst EM, de Soet JJ, Cenci MS, et al. The influence of different restorative materials on secondary caries development in situ. J Dent. 2014 Sep;42(9):1171-7.	Ineligible design
Wilson N, Lynch C. Amalgam and minimal intervention: an incompatible relationship. Prim Dent J. 2013 Oct;2(4):18.	Ineligible publication i.e., commentary
Gottlieb M. Restoring the difficult class II with composite. Todays FDA. 2013 Mar;25(2):18-21.	Ineligible publication i.e., narrative review
Maltz M, Jardim JJ, Mestrinho HD, Yamaguti PM, Podesta K, Moura MS, et al. Partial removal of carious dentine: a multicenter randomized controlled trial and 18-month follow-up results. Caries Res. 2013;47(2):103-9.	Ineligible intervention i.e., not dental restorations
Visalli G, Baluce B, La MS, Micale RT, Cingano L, De Flora S, et al. Genotoxic damage in the oral mucosa cells of subjects carrying restorative dental fillings. Arch Toxicol. 2013 Jan;87(1):179-87.	Ineligible timeframe i.e., published prior to 2012
Martin J, Fernandez E, Estay J, Gordan VV, Mjor IA, Moncada G. Minimal invasive treatment for defective restorations: five-year results using sealants. Oper Dent. 2013 Mar;38(2):125-33.	Ineligible population i.e., not caries
Maserejian NN, Hauser R, Tavares M, Trachtenberg FL, Shrader P, McKinlay S. Dental composites and amalgam and physical development in children. J Dent Res. 2012 Nov;91(11):1019-25.	Ineligible outcome i.e., not efficacy
Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, Bellinger DC. Dental composite restorations and neuropsychological development in children: treatment level analysis from a randomized clinical trial. Neurotoxicology. 2012 Oct;33(5):1291-7.	Ineligible outcome i.e., not efficacy
Kopperud SE, Tveit AB, Gaarden T, Sandvik L, Espelid I. Longevity of posterior dental restorations and reasons for failure. Eur J Oral Sci. 2012 Dec;120(6):539-48.	Ineligible design i.e., not an RCT
Dutra TT, Tapety ZI, Mendes RF, Moita Neto JM, Prado Junior RR. Survival time of direct dental restorations in adults. Rev odontol UNESP. 2015 Aug;44(4):213-7.	Ineligible design i.e., not an RCT
Cardoso RM, Cardoso RM, Gomes MP, Guimaraes RP, Menezes Filho PF, Silva CH. [Onlay with direct composite resin: a case report]. Odontol Clin -Cient. 2012 Sep;11(3):259-64. Portuguese.	Ineligible design i.e., not an RCT
de las N Laplace Perez B, Castellanos Amestoy L, Legra Matos SM, Peñuela Pérez EB, Fernández Laplace J. [Presentation of a patient with radicular perforation as a complication of endodontic treatment]. Correo Científico Médico de Holguín. 2015 Mar;19(1):166-72. Spanish.	Ineligible design i.e., not an RCT
Ceballos Casanova M, Acevedo Atala C, Jans Muñoz A, Atala Acevedo C. [Comparative study of the indicated survival rate of restorative materials used in pediatric patients 4 to 9 years of age with high risk of developing caries]. Int J Odontostomat. 2014 Dec;8(3):345-50. Spanish.	Ineligible design i.e., not an RCT
Biondi AM, Cortese SG. [Restitution of coronary integrity in primary parts]. Boletín de la Asociación Argentina de Odontologia para Niños. 2014 Aug;42/43(1):55-9.	Other i.e., cannot retrieve

Reference	Reason for Exclusion
Ferreira MG, Camapum MC, Ferreira GC, Silva JA, de Carvalho Cardoso P, Perillo MV. [Perspectiva restauradora para dentes tratados endodonticamente: pino anatômico]. Dent press endod. 2014 Apr;4(1):34-45. Portuguese.	Ineligible design i.e., not an RCT
Constâncio ST, de Souza Viana LB, Rodrigues Silva FC, da Silva JM, Gemaque ID. [Anatomic pins – description of the technique and radiographic control after six years]. Full Dentistry in Science. 2012 Sep;3(12):416-23. Portuguese.	Ineligible design i.e., not an RCT
Jardim JJ, Paula L, Garcia R, Mestrinho HD, Yamaguti P, Nascimento C. Restorations placed after partial caries removal - 36-month results [abstract]. Proceedings of the General Session of the International Association for Dental Research. 2012. (Presented at IADR 4531 general session; 2012 Jun 20-23; Iguacu Falls, BR).	Ineligible publication i.e., conference abstract

Research Question 2

Reference	Reason for Exclusion
Moller B, Granath LE. Reaction of the human dental pulp to silver amalgam restorations. The effect of insertion of amalgam of high plasticity in deep cavities. Acta Odontol Scand. 1973;31(3).	Ineligible timeframe i.e., published prior to 2007
Mortazavi SMJ, Mortazavi G, Paknahad M. Comment on Sundseth et al. Global sources and pathways of mercury in the context of human health. Int. J. Environ. Res. Public health 2017, 14, 105. Int J Environ Res Public Health. 2017;14(5).	Ineligible publication i.e., commentary
Cabaña-Muñoz ME, Parmigiani-Izquierdo JM, Bravo-González LA, Kyung HM, Merino JJ. Increased Zn/glutathione levels and higher superoxide dismutase-1 activity as biomarkers of oxidative stress in women with long-term dental amalgam fillings: correlation between mercury/aluminium levels (in hair) and antioxidant systems in plasma. PLoS One. 2015;10(6).	Ineligible comparison i.e., no composite resin
Bjorklund G, Bengtsson U, Chirumbolo S, Kern JK. Concerns about environmental mercury toxicity: do we forget something else? Environ Res. 2017;152:514-6.	Ineligible publication i.e., commentary
Bombeccari GP, Guzzi G, Spadari F, Gianni AB. Diagnosis of metal allergy and management of oral lichenoid reactions. J Oral Pathol Med. 2016;45(3):237-8.	Ineligible publication i.e., letter to the editor
Goulle JP, Guerbet M. [Is mercury from dental amalgams toxic?]. Toxicologie Analytique et Clinique. 2014;26(4):181-5. French.	Ineligible publication i.e., commentary
Zwicker JD, Dutton DJ, Emery JCH. Longitudinal analysis of the association between removal of dental amalgam, urine mercury and 14 self-reported health symptoms. Environ Health. 2014;13(1).	Ineligible comparison i.e., no composite resin
Geier DA, Carmody T, Kern JK, King PG, Geier MR. A dose-dependent relationship between mercury exposure from dental amalgams and urinary mercury levels: a further assessment of the Casa Pia Children's Dental Amalgam Trial. Hum Exp Toxicol. 2012;31(1):11-7.	Ineligible comparison i.e., no composite resin
Webster PC. Not all that glitters: mercury poisoning in Colombia. The Lancet. 2012;379(9824):1379-80.	Ineligible publication i.e., commentary
Maserejian NN, Tavares MA, Hayes C, Soncini JA, Trachtenberg FL. Prospective study of 5-year caries increment among children receiving comprehensive dental care in the New England Children's Amalgam Trial. Community Dent Oral Epidemiol. 2009;37(1):9-18.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Maserejian NN, Trachtenberg FL, Assmann SF, Barregard L. Dental amalgam exposure and urinary mercury levels in children: the New England Children's Amalgam Trial. Environ Health Perspect. 2008;116(2):256-62.	Ineligible comparison i.e., no composite resin
Daniels JL, Rowland AS, Longnecker MP, Crawford P, Golding J. Maternal dental history, child's birth outcome and early cognitive development: childhood outcomes. Paediatr Perinat Epidemiol. 2007;21(5):448-57.	Ineligible comparison i.e., no composite resin
Trachtenberg F, Barregard L. The effect of age, sex, and race on urinary markers of kidney	Ineligible population i.e., secondary

Reference	Reason for Exclusion
damage in children. Am J Kidney Dis. 2007;50(6):938-45.	analyses not considering originally randomized treatment groups
Yin L, Yu K, Lin S, Song X, Yu X. Associations of blood mercury, inorganic mercury, methyl mercury and bisphenol A with dental surface restorations in the U.S. population, NHANES 2003-2004 and 2010-2012. Ecotoxicol Environ Saf. 2016 Dec;134:213-25.	Ineligible comparison i.e., not comparing dental materials
Dutton DJ, Fyie K, Faris P, Brunel L, Emery JH. The association between amalgam dental surfaces and urinary mercury levels in a sample of Albertans, a prevalence study. J Occup Med Toxicol. 2013 Aug 29;8(1):22.	Ineligible comparison i.e., no composite resin
Mackert JR, Jr. Randomized controlled trial demonstrates that exposure to mercury from dental amalgam does not adversely affect neurological development in children. J Evid Based Dent Pract. 2010 Mar;10(1):25-9.	Ineligible publication i.e., commentary
Roumanas ED. The frequency of replacement of dental restorations may vary based on a number of variables, including type of material, size of the restoration, and caries risk of the patient. J Evid Based Dent Pract. 2010 Mar;10(1):23-4.	Ineligible publication i.e., commentary
Abt E. The risk of failure is higher for composites than for amalgam restorations. J Evid Based Dent Pract. 2008 Jun;8(2):83-4.	Ineligible publication i.e., commentary
Qasaymeh MM, Myers GJ. The safety of amalgam compared with resin composite restorations in children older than 6 years showed no significant differences on neurobehavioral or renal studies during a 5-year follow-up. J Evid-based Dent Pract. 2007 Sep;7(3):138-40.	Ineligible publication i.e., commentary
Qasaymeh MM, Myers GJ. The safety of amalgam compared with resin composite restorations in children older than 8 years showed no significant differences on neurobehavioral or nerve conduction studies during a 7-year follow-up. J Evid-based Dent Pract. 2006 Dec;6(4):280-2.	Ineligible publication i.e., commentary
Oviir T, Ibarra G. Amalgams lead to more catastrophic failures in endodontically treated premolars with class II cavities. J Evid Based Dent Pract. 2006 Jun;6(2):176-7.	Ineligible publication i.e., commentary
Bedir Findik R, Celik HT, Ersoy AO, Tasci Y, Moraloglu O, Karakaya J. Mercury concentration in maternal serum, cord blood, and placenta in patients with amalgam dental fillings: effects on fetal biometric measurements. J Matern Fetal Neonatal Med. 2016 Nov;29(22):3665-9.	Ineligible comparison i.e., cannot ascertain composite resin
Golding J, Steer CD, Gregory S, Lowery T, Hibbeln JR, Taylor CM. Dental associations with blood mercury in pregnant women. Community Dent Oral Epidemiol. 2016 Jun;44(3):216-22.	Ineligible comparison i.e., no composite resin
Pigatto PD, Spadari F, Bombeccari GP, Guzzi G. Oral lichenoid reactions, patch tests, and mercury dental amalgam. J Oral Pathol Med. 2016 Feb;45(2):153.	Ineligible publication i.e., letter to the editor
Rooney JP, Frissen MN, Bass GA, Dorea JG. Dental amalgam fillings and Helicobacter pylori eradication rates: wide-ranging implications. Eur J Gastroenterol Hepatol. 2015 Oct;27(10):1231.	Ineligible publication i.e., letter to the editor
Sakallioglu EE, Lutfioglu M, Sakallioglu U, Ceylan GK, Pamuk F, Dede FO, et al. Gingival crevicular fluid levels of neuropeptides following dental restorations. J Appl Biomater Function Mater. 2015 Jul 4;13(2):e186-e193.	Ineligible outcome i.e., not safety
Kwang S, Aminoshariae A, Harding J, Montagnese TA, Mickel A. The critical time-lapse between various restoration placements and subsequent endodontic intervention. J Endod. 2014 Dec;40(12):1922-6.	Ineligible outcome i.e., not safety
Woods JS, Heyer NJ, Russo JE, Martin MD, Farin FM. Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology. 2014 Sep;44:288-302.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Maserejian NN, Shrader P, Trachtenberg FL, Hauser R, Bellinger DC, Tavares M. Dental sealants and flowable composite restorations and psychosocial, neuropsychological, and physical development in children. Pediatr Dent. 2014 Jan;36(1):68-75.	Ineligible intervention i.e., sealants
Woods JS, Heyer NJ, Russo JE, Martin MD, Pillai PB, Bammler TK, et al. Genetic polymorphisms of catechol-O-methyltransferase modify the neurobehavioral effects of mercury in children. J Toxicol Environ Health A. 2014;77(6):293-312.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups

Reference	Reason for Exclusion
Trachtenberg FL, Shrader P, Barregard L, Maserejian NN. Dental composite materials and renal function in children. Br Dent J. 2014 Jan;216(2):E4.	Ineligible comparison i.e., no amalgam
Visalli G, Baluce B, La MS, Micale RT, Cingano L, De FS, et al. Genotoxic damage in the oral mucosal cells of subjects carrying restorative dental fillings. Arch Toxicol. 2013 Dec;87(12):2247-8.	Ineligible publication i.e., letter to the editor
Watson GE, van Wijngaarden E, Love TM, McSorley EM, Bonham MP, Mulhern MS, et al. Neurodevelopmental outcomes at 5 years in children exposed prenatally to maternal dental amalgam: the Seychelles Child Development Nutrition Study. Neurotoxicol Teratol. 2013 Sep;39:57-62.	Ineligible comparison i.e., no composite resin
Woods JS, Heyer NJ, Russo JE, Martin MD, Pillai PB, Farin FM. Modification of neurobehavioral effects of mercury by genetic polymorphisms of metallothionein in children. Neurotoxicol Teratol. 2013 Sep;39:36-44.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Correa MB, Peres MA, Peres KG, Horta BL, Barros AJ, Demarco FF. Do socioeconomic determinants affect the quality of posterior dental restorations? A multilevel approach. J Dent. 2013 Nov;41(11):960-7.	Ineligible outcome i.e., not safety
Geier DA, Carmody T, Kern JK, King PG, Geier MR. A significant dose-dependent relationship between mercury exposure from dental amalgams and kidney integrity biomarkers: a further assessment of the Casa Pia Children's Dental Amalgam Trial. Hum Exp Toxicol. 2013 Apr;32(4):434-40.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Visalli G, Baluce B, La MS, Micale RT, Cingano L, De Flora S, et al. Genotoxic damage in the oral mucosa cells of subjects carrying restorative dental fillings. Arch Toxicol. 2013 Jan;87(1):179-87.	Ineligible population i.e., no explicit comparison of composite resin and amalgam
Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, Tavares M, et al. Dental composite restorations and psychosocial function in children. Pediatrics. 2012 Aug;130(2):e328-e338.	Ineligible comparison i.e., no amalgam
Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, Bellinger DC. Dental composite restorations and neuropsychological development in children: treatment level analysis from a randomized clinical trial. Neurotoxicology. 2012 Oct;33(5):1291-7.	Ineligible comparison i.e., no amalgam
Dental restoration materials and physical development in children. J Can Dent Assoc. 2012;78:-c138.	Ineligible publication i.e., not a report of study findings
Watson GE, Evans K, Thurston SW, van WE, Wallace JM, McSorley EM, et al. Prenatal exposure to dental amalgam in the Seychelles Child Development Nutrition Study: associations with neurodevelopmental outcomes at 9 and 30 months. Neurotoxicology. 2012 Dec;33(6):1511-7.	Ineligible comparison i.e., no composite resin
Ababnaeh KT, Al-Omari M, Alawneh TN. The effect of dental restoration type and material on periodontal health. Oral Health Prev Dent. 2011;9(4):395-403.	Ineligible outcome i.e., not safety
Al-Saleh I, Al-Sedairi AA. Mercury (Hg) burden in children: the impact of dental amalgam. Sci Total Environ. 2011 Jul 15;409(16):3003-15.	Ineligible comparison i.e., no composite resin
Geier DA, Carmody T, Kern JK, King PG, Geier MR. A significant relationship between mercury exposure from dental amalgams and urinary porphyrins: a further assessment of the Casa Pia Children's Dental Amalgam Trial. Biometals. 2011 Apr;24(2):215-24.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Lygre GB, Bjorkman L, Haug K, Skjaerven R, Helland V. Exposure to dental amalgam restorations in pregnant women. Community Dent Oral Epidemiol. 2010 Oct;38(5):460-9.	Ineligible comparison i.e., no composite resin
Trachtenberg F, Barregard L, McKinlay S. The influence of urinary flow rate on mercury excretion in children. J Trace Elem Med Biol. 2010 Jan;24(1):31-5.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Surkan PJ, Wypij D, Trachtenberg F, Daniel DB, Barregard L, McKinlay S, et al. Neuropsychological function in school-age children with low mercury exposures. Environ Res. 2009 Aug;109(6):728-33.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Ye X, Qian H, Xu P, Zhu L, Longnecker MP, Fu H. Nephrotoxicity, neurotoxicity, and mercury exposure among children with and without dental amalgam fillings. Int J Hyg Environ Health. 2009 Jul;212(4):378-86.	Ineligible comparison i.e., no composite resin
Rothwell JA, Boyd PJ. Amalgam dental fillings and hearing loss. Int J Audiol. 2008 Dec;47(12):770-6.	Ineligible comparison i.e., no explicit comparison of composite resin and

Reference	Reason for Exclusion
	amalgam
Hajizadeh H, Akbari M, Ghavamnasiri M, Abedini S. Clinical evaluation of a resin-based desensitizing agent and a self-etching adhesive on the reduction of postoperative sensitivity of amalgam restorations. J Contemp Dent Pract. 2008 Nov 1;9(7):9-16.	Ineligible intervention i.e., liners (not restorations)
Di PA, Visalli G, La MS, Micale R, Baluce B, Matarese G, et al. Biomonitoring of DNA damage in peripheral blood lymphocytes of subjects with dental restorative fillings. Mutat Res. 2008 Feb 29;650(2):115-22.	Ineligible comparison i.e., no explicit comparison of composite resin and amalgam
Dunn JE, Trachtenberg FL, Barregard L, Bellinger D, McKinlay S. Scalp hair and urine mercury content of children in the Northeast United States: the New England Children's Amalgam Trial. Environ Res. 2008 May;107(1):79-88.	Ineligible comparison i.e., no explicit comparison of composite resin and amalgam
Surkan PJ, Zhang A, Trachtenberg F, Daniel DB, McKinlay S, Bellinger DC. Neuropsychological function in children with blood lead levels <10 microg/dL. Neurotoxicology. 2007 Nov;28(6):1170-7.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: the New England Children's Amalgam Trial. J Am Dent Assoc. 2007 Sep;138(9):1210-6.	Ineligible population i.e., secondary analyses not considering originally randomized treatment groups
Bernardo M, Luis H, Martin MD, Leroux BG, Rue T, Leitao J, et al. Survival and reasons for failure of amalgam versus composite posterior restorations placed in a randomized clinical trial. J Am Dent Assoc. 2007 Jun;138(6):775-83.	Ineligible outcome i.e., not safety
DeRouen TA, Martin MD, Leroux BG, Townes BD, Woods JS, Leitao J, et al. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006 Apr 19;295(15):1784-92.	Ineligible timeframe i.e., published prior to 2007
Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E, Daniel D, et al. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006 Apr 19;295(15):1775-83.	Ineligible timeframe i.e., published prior to 2007
Whitworth JM, Myers PM, Smith J, Walls AW, McCabe JF. Endodontic complications after plastic restorations in general practice. Int Endod J. 2005 Jun;38(6):409-16	Ineligible timeframe i.e., published prior to 2007
Evens CC, Martin MD, Woods JS, Soares HL, Bernardo M, Leitao J, et al. Examination of dietary methylmercury exposure in the Casa Pia Study of the health effects of dental amalgams in children. J Toxicol Environ Health A. 2001 Dec 7;64(7):521-30.	Ineligible timeframe i.e., published prior to 2007

Appendix 7: Critical Appraisal — Clinical Review

Research Question 1

	Random sequence generation	Allocation concealment	Blinding participants & personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
Kemaloglu 2016 [36]	+	?	—	—	?	?	—

+ = low risk of bias; ? = unclear risk of bias; — = high risk of bias

Research Question 2

		Random sequence generation	Allocation concealment	Blinding participants & personnel	Blinding outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
NECAT	Barregard, 2008 [42]	+	+	—	+	—	+	+
	Bellinger, 2007 [45]	+	+	—	+	+	+	?
	Bellinger 2008 [38]	+	+	—	+	+	+	+
	Maserejian 2012 [37]	+	+	—	+	+	+	+
	Shenker 2008 [40]	?	?	—	+	?	—	+
Casa Pia	Lauterbach 2008 [43]	?	?	—	?	—	—	+
	Woods 2007 [44]	?	?	—	?	?	+	?
	Woods 2008 [41]	?	?	—	?	?	+	+
	Woods 2009 [39]	?	?	—	?	?	—	+
	Kemaloglu 2016 [36]	+	?	—	?	?	?	—

+ = low risk of bias; ? = unclear risk of bias; — = high risk of bias

Appendix 8: Study and Report Characteristics — Clinical Review

Research Question 1

Table 20: Summary of Characteristics for the 2014 Systematic Review

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number of included studies and design	Number of teeth and duration of follow-up for included studies	Intervention and Comparator, or Exposure(s)	Eligible Outcomes and Measures Reported	Subgroup Analyses
Rasines Alcaraz Argentina No internal source of financial support reported	Systematic Review Assessment of between-study heterogeneity to inform decisions regarding quantitative synthesis	N=7 RCTs n=2 parallel group RCTs (pooled for primary analysis) n=5 split-mouth RCTs	N=3,010 permanent, posterior teeth included in primary analysis 3-year minimum follow up Range of follow up=3 to 7 yrs	Amalgam vs. Composite resin dental restorations	Restoration failure, which includes: (i) secondary caries (ii) restoration fracture (iii) restoration loss	Split-mouth studies analyzed separately from parallel group RCTs

Table 21: Summary of Characteristics from the Study Included in the 2017 Systematic Review Update

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number of teeth and/or /restorations	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes and Measures Reported	Subgroup Analyses
Kemaloglu 2016[36] Turkey Financial support reported as “Nil” (p. 22)	Single-centre RCT, split-mouth design Proportion of restorations per treatment group rated as Alpha, Bravo, Charlie tallied and overall failure rate	N=50 teeth randomized Amalgam = 20 restorations Composite = 20 restorations	Study duration = 3yr Median follow-up = NR Follow-up evaluations at 2wks, 6mos,	Dispersed alloy amalgam (Cavex) placed with Amalgambond bonding agent Posterior resin composite	1. Restoration performance (i.e., retention, marginal adaptation, anatomic form, surface texture and secondary caries) measured at baseline (i.e., 2wks post-intervention), 6, 12 and 36mos i.e., (i) Modified US Public Health Service (USPHS) Ryge criteria, Alpha (best), Bravo, Charlie (worst) assessed by two evaluators not involved in placing the	None

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number of teeth and/or /restorations	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes and Measures Reported	Subgroup Analyses
	calculated		1 and 3yrs Loss to F/U = 5/25 consented patients (analyses based on 40 teeth)	(Quixfil) placed with etch-and-rinse adhesive system (XP Bond)	restorations (ii) Inter-rater agreement, Cohen's Kappa (iii) Overall failure, calculated as: (previous failures + new failures)/(previous failures + currently recalled restorations)	

Research Question 2

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
Kemaloglu 2016[36] Turkey Financial support reported as "Nil" (p. 22)	Single-centre RCT, split-mouth design Difference in post-operative sensitivity evaluated by treatment group using Wilcoxon signed rank test	N=20 participants N=40 teeth, Amalgam = 20 teeth, Composite = 20 teeth Age range = 18-60yrs Sex = NR	Study duration = 3yr Median follow-up = NR Follow-up evaluations at 2wks, 6mos, 1 and 3yrs Loss to F/U = 5/25 consented patients (analyses based on 20 patients with 40 teeth)	Dispersed alloy amalgam (Cavex) placed with Amalgambond bonding agent Posterior resin composite (Quixfil) placed with etch-and-rinse adhesive system (XP Bond)	1. Post-operative sensitivity, measured actively at baseline, 6, 12 and 36mos i.e., (i) Visual Analog Scale (VAS) 0-10	None

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
Bellinger, 2007[45] USA Trial funded by a cooperative agreement, (U01 DE11886), between the New England Research Institutes and the National Institute of Dental and Craniofacial Research	Multi-centre RCT (NECAT) stratified by geographic location and number of teeth with caries (2–4 vs. ≥ 5), using randomly permuted blocks within each stratum ITT analyses using ANCOVA adjusted for randomization stratum, age, sex, race, socioeconomic status, baseline hair mercury level, baseline blood lead level, lean body mass, type of specimen (overnight vs. spot daytime urine sample), urinary creatinine concentration, storage time, and baseline γ-GT (for γ-GT models only)	N=534 (variable numbers analyzed per measure/ subscale) Amalgam = 267 Composite = 267 Age in years, mean (SD) range Amalgam = 7.9 (1.3) 5.9-11.4 Composite = 7.9 (1.4) 5.9-11.5 Amalgam, female: 131, 49.1% Composite, female: 156, 58.4%	Study duration = 5yr Semi-annual visits Follow-up = NR Loss to F/U = NR	Dispersed phase amalgam Resin composite material (white filling)	1. Amalgam exposure, measured actively i.e., (i) Mean number of restored surfaces (ii) Mean number of amalgam surfaces (iii) Cumulative number of restored surfaces (5yr follow up) (iv) Cumulative number of amalgam surfaces 2. Urinary elemental mercury levels, measured actively i.e., (i) mcg/g creatinine 3. Neuropsychological function i.e., active, annual administration of ≥1 of the following tests: (i) Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (ii) Wechsler Individual Achievement Test (WIAT) (iii) Wide Range Assessment of Memory and Learning (WRAML) (iv) Wide Range Assessment of Visual–Motor Ability (WRAVMA) (v) Trail-Making Test (vi) WPS Electronic Tapping Test (vii) ordered and unordered verbal cancellation (viii) category fluency (ix) Controlled Oral Word Association Test (x) Simple visual reaction time (xi) Stroop Color-Word Interference Test (xii) Wisconsin Card Sorting Test	None
Bellinger 2008[38]	Multi-centre RCT (NECAT) stratified by	N = 534 (N = 395 included in	Study duration = 5yr	Dispersed-phase amalgam	1. Psychosocial function measured actively i.e., (i) Child Behavior Checklist (CBCL),	None

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
USA Trial supported by a cooperative agreement (U01 DE11886) between the New England Research Institutes and the National Institute of Dental and Craniofacial Research	geographic location and number of teeth with caries (2 to 4 vs. ≥ 5), with randomly permuted blocks within each stratum Analyses using ANCOVA adjusted for baseline score, age, gender, race, socio-economic status, primary caregiver's marital status, birth weight, maternal exposure during pregnancy to tobacco, alcohol, and drugs, family stress, baseline child Full-Scale IQ, and randomization stratum	the CBCL analyses, Amalgam = 197, Composite = 198; N=426 included in the BASC-SR analyses, Amalgam n= 213, Composite n = 213) Age in years, mean (SD) range Amalgam = 7.9 (1.4) 6.1-11.5 Composite = 7.8 (1.3) 6.0-11.2 Amalgam, female: 96/197, 48.7% Composite female: 106/198, 53.5%	Semi-annual visits Median follow-up = NR Loss to F/U = NR	Composite resin	change in scores, measured at baseline and 5yrs – primary outcome, parent-reported (ii) Behavior Assessment System for Children (BASC-SR) measured at 5yrs – secondary outcome, child-reported	
Lauterbach 2008[43] Portugal Trial funded by the National Institute of Dental Craniofacial Research	RCT (Casa Pia) Descriptive, unadjusted analyses with comparisons using Fisher's exact test (proportions) and two-sample Student t-test (means)	N = 507 (N = 506 included in this analysis Amalgam = 253 Composite = 253) Age in years, mean (SD) Amalgam = 10.2 (0.98) Composite = 10.1	Study duration = 7yr Median follow-up = NR Annual neurological evaluations Loss to F/U =	Dental amalgam (posterior restorations; resin-based composite restorations elsewhere) Composite restorations only	1. Neurological hard signs (NHS), active, annual assessment of absence/presence within 8 categories: (i) mental status (consciousness; language; and orientation to person, time and place) (ii) observation of the function of the 12 cranial nerves (iii) gross motor function (muscle strength and tone and deep tendon reflexes) (iv) plantar responses	None

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
Cooperative Agreement grant U01 DE11894; additional funding from the National Institute of Environmental Health Sciences via the University of Washington (Center grant P30ES07033 and by Superfund Program Project grant P42ES04696)		(0.94) Amalgam, female: 116/253, 45.8% Composite, female: 112/253, 44.3%	NR		(v) cerebellar functions (including limb and gait coordination) (vi) touch (vii) joint position and vibration senses (viii) involuntary movements (such as athetosis or chorea) 2. Positional tremor, active, annual assessment of absence/presence 3. Neurological soft signs (NSS), active, annual assessment of absence/presence and severity (i.e., 0 to 3) of 6 features: (i) mirror movements (ii) synkinesias (iii) clumsiness of fine finger movements (iv) tandem gait (v) motor impersistence (vi) restlessness/hyperactivity	
Shenker 2008[40] USA Analyses supported by USPHS grant N01 DE 72622	Multi-centre RCT (NECAT) ANCOVA adjusted for baseline corresponding immune function measurement, age, gender, socioeconomic status, hair mercury, and blood lead level	N=534 (N = 66 randomized into this sub-study; N = 59 included in the analyses, Amalgam = 29, Composite = 30) Age in years, mean (SD) Amalgam = 8.1 (1.3) Composite = 8.0 (1.4) Amalgam, female:	Study duration = 5yr Median follow-up = NR Semi-annual visits Loss to F/U = 5/66 Amalgam = 4 Composite = 1	Amalgam (i.e., Dispersalloy) Resin-based composite (i.e., Z100)	1. Amalgam exposure, measured actively and annually (i) Number of surfaces restored with amalgam 2. Urinary elemental mercury levels, measured actively and annually i.e., (i) mcg/g creatinine 3. Immune function i.e., values measured actively at baseline, 5-7 days, 6, 12 and 60 months post-intervention (i) White blood cell (WBC) count (ii) T-cell function following incubation with phytohemagglutinin (PHA), 5 mcg/ml	None

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
		10/29 (34.5%) Composite, female: 19/30 (63.3%)			a. CD25 activation marker expression (%CD25+ (PHA)) b. CD69 activation marker expression (%CD69+ (PHA)) c. cell cycle distribution (iii) B-cell function following stimulation with pokeweed mitogen (PWM), 10 mcg/ml a. CD23 activation marker expression (%CD23+ (PHA)) b. CD69 activation marker expression (%CD69+ (PWM)) (iv) Monocyte and neutrophil function by measuring phorbol myristate acetate (PMA), 0.5 mcg/ml-induced oxidative burst a. O_2 generation assessed by dihydroethidium fluorescent probe (% Eth+(PMA)) b. H_2O_2 generation assessed by dihydrorhodmine fluorescent probe (% Rho+(PMA))	
Barregard, 2008[42] USA Trial funded by the National Institute of Dental and Craniofacial Research (U01 DE11886)	Multi-centre RCT (NECAT) stratified by geographic location and number of teeth with caries (2–4 vs. ≥ 5) Repeated-measures analyses using ANCOVA and logistic regression models adjusted for randomization stratum, age, sex,	N=534 (N=490 included in this analysis) Amalgam = 267 Composite = 267 Age in years, mean (SD) range Amalgam = 7.9 (1.3) 5.9-11.4 Composite = 7.9 (1.4) 5.9-11.5	Study duration = 5yr Semi-annual visits Median follow-up = NR Loss to F/U = 19% at 5yr	Dispersed phase amalgam Resin composite material (white filling)	1. Renal biomarkers, measured actively i.e., urinary excretion at yrs 1 (γ-GT only), 3 and 5 of: (i) albumin (mg/g creatinine) (ii) alpha-1-microglobulin (A1M) (mg/g creatinine) (iii) γ-glutamyl transpeptidase (γ-GT) (U/g creatinine) (iv) N-acetyl-β-D-glucosaminidase (NAG) (U/g creatinine)	None

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
	race, socioeconomic status, baseline hair mercury level, baseline blood lead level, lean body mass, type of specimen (overnight vs. spot daytime urine sample), urinary creatinine concentration, storage time, and baseline γ-GT (for γ-GT models only)	Amalgam, female: 131/267, 49.1% Composite female: 156/267, 58.4%				
Woods 2008[41] Portugal Trial funded by the National Institute of Dental Craniofacial Research Cooperative Agreement grant U01 DE11894; additional funding from the National Institute of Environmental Health Sciences	RCT (Casa Pia) Descriptive statistics for log-transformed concentrations of renal biomarkers; linear regression models, (i) unadjusted and (ii) adjusted for log-transformed creatinine concentration in the sample, year of age (i.e., 9-18, ordinal), age at baseline (i.e., years), sex and race (i.e., 'white' versus 'non-white')	N=507 Age range = 8-12 Female = 46% Male = 54%	Study duration = 7yr Median follow-up = NR Loss to F/U = NR	Amalgam Composite resin	1. Urinary mercury at baseline, measured actively i.e., mcg/g creatinine 2. Renal function measured actively per annual age cohort i.e., urinary: (i) Glutathione S-transferases (GST)-α i.e., mcg/g creatinine (ii) Glutathione S-transferases (GST)-π i.e., mcg/g creatinine (iii) albumin i.e., mg/g creatinine (iv) microalbuminuria i.e., proportion of participants with albumin >30 mg/g creatinine	Treatment group and sex

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
via the University of Washington (Center grant P30ES07033 and by Superfund Program Project grant P42ES04696)						
Maserejian 2012[37] USA Analyses funded by Award Number R01ES019155 from the National Institute of Environmental Health Sciences (NIEHS); data collection supported by a cooperative agreement (U01 DE11886) between the New England Research Institutes and	Multi-centre RCT (NECAT) stratified by number of teeth with caries (2-4 vs. ≥ 5) and rural/urban location ITT using linear mixed-effects, repeated-measures regression models adjusted for randomization stratum, age, and relevant baseline anthropometric measure	N = 534 (N = 474 included in these analyses, Amalgam = 238, Composite = 236) Age in years, mean (SD) Amalgam = 7.5 (1.3) Composite = 7.4 (1.4) Amalgam, female: 121/238, 50.8% Composite, female: 135/236, 57.2%	Study duration = 5yr Median follow-up = NR Loss to F/U, Amalgam n= 24 Composite n=26	Amalgam (i.e., Dispersalloy) Resin-based composite (i.e., Z100)	1. Physical development in males and in females, measured annually and actively and presented as 5-year changes in: (i) BMI (kg/m^2)-for-age Z-score (ii) Body fat (%) (iii) Height (cm) (iv) Menarche (females from 1 site only) • Number who reached menarche • Age at first menarche	All analyses run in consideration of sex

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
the National Institute of Dental and Craniofacial Research (NIDCR)						
Woods 2007[44] Portugal Trial funded by the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health through Cooperative Agreement U01DE11894	RCT (Casa Pia) Descriptive i.e., means, 95% CIs and t-tests for treatment group comparisons	N=507 (Amalgam = 253, Composite = 254) Age in years, mean (SD) range Amalgam = 10.1 (1.0) 8.0-12.4 Composite = 10.0 (0.9) 8.2-12.0 Amalgam, female: 116/253, 46% Composite, female: 112/254, 44%	Study duration = 7yr Median follow-up = NR Annual visits Loss to F/U = NR	Amalgam (i.e., Dispersalloy) Composite resin	1. Urinary mercury actively measured annually: (i) unadjusted mcg/L (ii) creatinine-adjusted mcg/g	Treatment group, race, sex and number of amalgam surface areas
Woods 2009[39] Portugal Trial funded by the National Institute of Dental Craniofacial Research Cooperative	RCT (Casa Pia) Mixed, linear regression models adjusted for age, sex, race (white/non-white), follow-up year, log-transformed urinary creatinine, and baseline log-transformed	N=507 Age range = 8-12 Female = 46% Male = 54%	Study duration = 7yr Median follow-up = NR Loss to F/U = NR	Amalgam Composite resin	1. Urinary mercury at baseline, measured actively and annually i.e., (i) mcg/g creatinine 2. Urinary porphyrins, measured actively and annually i.e., (i) log-transformed mcg/L	8 and 9 year olds only

First Author, Publication Year, Country, Funding Source	Study Design, Analytical Method	Number, Age, Sex, of Study Patients	Study Duration, Follow-Up, Loss to Follow-up	Intervention and Comparator, or Exposure(s)	Eligible Outcomes, Ascertainment of Harm(s), Measurement Time Points, and Measures Reported	Subgroup Analyses
Agreement grant U01 DE11894; additional funding from the National Institute of Environmental Health Sciences via the University of Washington (Center grant P30ES07033 and by Superfund Program Project grant P42ES04696)	porphyrin/creatinine ratio					

Appendix 9: Detailed Outcome Data — Clinical Review

Summary of Efficacy Outcomes (Research Question 1)

Table 22: Efficacy Outcomes Reported in the 2014 Systematic Review

Systematic Review Updated	Quantitative Findings (Primary Analyses)	Authors' Conclusions
Rasines Alcaraz 2014[6]	1. Restoration failure • Primary analysis (i.e., 2 parallel-group RCTs) ○ Casa Pia ▪ Amalgam • 48 failures (of 856 restorations analyzed) ▪ Composite resin • 129 failures (of 892 restorations analyzed) ▪ RR 2.58 (95% CI: 1.88 to 3.54) ○ NECAT ▪ Amalgam • 55 failures (of 509 restorations analyzed) ▪ Composite resin • 112 failures (of 753 restorations analyzed) ▪ RR 1.38 (95% CI: 1.02 to 1.86) ○ Overall pooled estimate (fixed effects) ▪ RR 1.89 (95% CI 1.52 to 2.35) ○ Assumed risk per 1,000* ▪ Amalgam, 75 (95% CI: NR) ○ Corresponding risk per 1,000* ▪ Composite resin, 142 (95% CI: 114-176) • Subgroup analysis (i.e., 5 split-mouth RCTs) ○ Overall pooled estimate (random effects) ▪ RR 1.33 (95% CI: 0.84 to 2.11) 2. Secondary caries • Primary analysis (i.e., 2 parallel-group RCTs) ○ Casa Pia ▪ Amalgam • 32 occurences (of 856 restorations analyzed) ▪ Composite resin • 113 occurences (of 892 restorations analyzed) ▪ RR 3.39 (95% CI 2.31 to 4.96)	"There is low-quality evidence to suggest that resin composites lead to higher failure rates and risk of secondary caries than amalgam restorations. This review reinforces the benefit of amalgam restorations and the results are particularly useful in parts of the world where amalgam is still the material of choice to restore posterior teeth with proximal caries."

Systematic Review Updated	Quantitative Findings (Primary Analyses)	Authors' Conclusions
	○ NECAT ▪ Amalgam • 46 occurences (of 509 restorations analyzed) ▪ Composite resin • 95 occurences (of 753 restorations analyzed) ▪ RR 1.40 (95% CI 1.00 to 1.95) ○ Overall pooled estimate ▪ RR 2.14 (95% CI 1.67 to 2.74) ○ Assumed risk per 1,000* ▪ Amalgam, 57 (95% CI NR) ○ Corresponding risk per 1,000* ▪ Composite resin, 122 (95% CI: 95 to 156) • Subgroup analysis (i.e., 5 split-mouth RCTs) ○ Overall pooled estimate (random effects) ▪ RR 1.3 (95% CI: 0.34 to 4.97) 3. Restoration fracture • Per-study estimates ○ Casa Pia ▪ Amalgam • 16 occurences (of 856 restorations analyzed) ▪ Composite resin • 16 occurences (of 892 restorations analyzed) ▪ RR 0.96 (95% CI 0.48 to 1.91) ○ NECAT ▪ Amalgam • 3 occurences (of 509 restorations analyzed) ▪ Composite resin • 2 occurences (of 753 restorations analyzed) ▪ RR 0.45 (95% CI 0.08 to 2.69) ○ Overall pooled estimate ▪ RR 0.87 (95% CI 0.46 to 1.64) ○ Assumed risk per 1,000* ▪ Amalgam, 14 (95% CI NR) ○ Corresponding risk per 1,000* ▪ Composite resin, 12 (95% CI: 6 to 23) • Subgroup analysis (i.e., 5 split-mouth RCTs) ▪ NR	

*Methods informing the calculation of assumed and corresponding risk for amalgam and composite resin, respectively, were not elaborated

Table 23: Efficacy Outcomes Reported by the Study Included in the 2017 Systematic Review Update

Eligible Study from 2017 Update	Quantitative Findings or Narrative Summary	Authors' Conclusions
Kemaloglu 2016[36]	1. Restoration performance (Modified USPHS (Ryge) criteria), % restorations rated Alpha and Bravo at baseline, 6, 12 and 36mos • Amalgam ○ Retention ▪ Alpha, 100, 100, 100, 100 ▪ Bravo, 0, 0, 0, 0 ○ Marginal adaptation ▪ Alpha, 100, 100, 90, 85 ▪ Bravo, 0, 0, 10, 15 ○ Anatomical form ▪ Alpha, 100, 100, 85, 50 ▪ Bravo, 0, 0, 15, 50 ○ Marginal discoloration ▪ Alpha, 100, 100, 95, 95 ▪ Bravo, 0, 0, 5, 5 ○ Surface texture ▪ Alpha, 100, 100, 75, 40 ▪ Bravo, 0, 0, 25, 60 ○ Secondary caries ▪ Alpha, 100, 100, 100, 100 ▪ Bravo, 0, 0, 0, 0 • Composite ○ Retention ▪ Alpha, 100, 100, 100, 100 ▪ Bravo, 0, 0, 0, 0 ○ Marginal adaptation ▪ Alpha, 100, 100, 90, 80 ▪ Bravo, 0, 0, 10, 20 ○ Anatomical form ▪ Alpha, 100, 100, 95, 75 ▪ Bravo, 0, 0, 5, 25 ○ Marginal discoloration ▪ Alpha, 100, 100, 80, 70 ▪ Bravo, 0, 0, 20, 30 ○ Surface texture	"In our study, the clinical success of bonded amalgam and direct resin composite restorations in deep and large sized cavities was evaluated for 3 years. Judging from the results, survival rate was 100% for both of the restoration types and they were found to be successful."

Eligible Study from 2017 Update	Quantitative Findings or Narrative Summary	Authors' Conclusions
	▪ Alpha, 100, 100, 65, 35 ▪ Bravo, 0, 0, 35, 65 ○ Secondary caries ▪ Alpha, 100, 100, 100, 100 ▪ Bravo, 0, 0, 0, 0 2. Inter-rater agreement for all restorations, Cohen's Kappa • 0.97 3. Overall failure, proportion of restorations • Detailed calculation NR • Reported as: "Overall failure rate of this study was 0% (100% acceptance for 3 years)…" (p. 19) for both groups	

mos = months

Summary of Safety Outcomes (Research Question 2)

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	Toxicity Outcomes	
Bellinger, 2007[45]	1. Neuropsychological function, change in score from baseline/1yr to end of study follow-up i.e., 4/5 years • WISC-III, adjusted mean coefficient ±SE (n) ○ Verbal Comprehension ▪ Amalgam, 2.2 ± 0.6 (219) ▪ Composite, 1.5 ± 0.6 (217) ○ Perceptual Organization ▪ Amalgam, 3.6 ± 0.7 (219) ▪ Composite, 3.1 ± 0.7 (216) ○ Freedom from Distractibility ▪ Amalgam, 3.9 ± 0.7 (219) ▪ Composite, 2.4 ± 0.7 (216) ○ Processing Speed ▪ Amalgam, 7.2 ± 0.9 (216) ▪ Composite, 5.1 ± 0.9 (217) ○ **No significant difference (ANCOVA) between groups, all subscales *P* = NS** • WIAT, adjusted mean coefficient ±SE (n) ○ Reading ▪ Amalgam, –1.0 ± 0.7 (217) ▪ Composite, –1.7 ± 0.7 (215) ○ Mathematics ▪ Amalgam, –1.9 ± 0.7 (216) ▪ Composite, –3.0 ± 0.8 (207) ○ **No significant difference (ANCOVA) between groups, all scales and subscales *P* = NS** • WRAML, adjusted mean coefficient ±SE (n) ○ Verbal Memory Index ▪ Amalgam, 2.9 ± 0.6 (212) ▪ Composite, 2.2 ± 0.6 (202) ○ Visual Memory Index ▪ Amalgam, 6.3 ± 0.8 (212) ▪ Composite, 5.0 ± 0.8 (204) ○ Learning Index ▪ Amalgam, 10.2 ± 0.8 (212) ▪ Composite, 10.3 ± 0.8 (203) ○ Number-Letter Memory subscale	"Exposure to elemental mercury in amalgam at the levels experienced by the children who participated in the trial did not result in significant effects on neuropsychological function within the 5-year follow-up period."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	▪ Amalgam, 0.3 ± 0.1 (212) ▪ Composite, –0.3 ± 0.1 (203) ▪ **Significant difference (ANCOVA, ITT) between groups favours amalgam *P* = 0.002** ○ **No significant difference (ANCOVA) between groups, all indices and other subscales, *P* = NS** • WRAVMA, adjusted mean coefficient ±SE (n) ○ Drawing ▪ Amalgam, –3.8 ± 0.9 (211) ▪ Composite, –3.1 ± 0.9 (203) ○ Matching ▪ Amalgam, 3.0 ± 0.8 (211) ▪ Composite, 3.5 ± 0.8 (203) ○ Pegboard ▪ Amalgam, 9.3 ± 0.9 (211) ▪ Composite, 8.4 ± 1.0 (203) ○ **No significant difference (ANCOVA) between groups, all scales, *P* = NS** • Trail-Making Test, adjusted mean coefficient ±SE (n) ○ Part B: time to complete ▪ Amalgam, –45.6 ± 1.0 (201) ▪ Composite, –50.4 ± 1.1 (193) ▪ **Significant difference (ANCOVA, ITT) between groups favours composite resin, *P* = 0.002** ○ **No significant difference (ANCOVA) between groups, Parts A, C, D, *P* = NS** • All other secondary outcome measures ○ **No significant difference (ANCOVA) between groups, *P* = NS** 2. Amalgam exposure at 5yr follow-up, mean ±SD (range) • Restored surfaces ○ Amalgam, 5.3 ± 5.2 (0–36) ○ Composite, 6.1 ± 6.0 (0–36) ○ **No significant difference (method NR) between groups *P* = 0.16** • Restored amalgam surfaces ○ Amalgam, 4.0 ± 4.0 (0–21) ○ Composite, 0.05 ± 0.6 (0–9) ○ ***P* = NR** • Cumulative restored surfaces ○ Amalgam, 14.8 ± 9.5 (2–55) ○ Composite, 16.0 ± 9.8 (2–51)	

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ **No significant difference (method NR) between groups *P* = 0.10** • Cumulative restored amalgam surfaces ○ Amalgam, 11.7 ± 7.0 (0–35) ○ Composite, 0.05 ± 0.6 (0–9) ○ ***P* = NR** 3. Urinary elemental mercury levels at 5yr follow up, median (range) • Amalgam, 0.9 (0.1-5.7) • Composite, 0.6 (0.1-2.9) • **Significant difference (method NR) between groups *P* < 0.001**	
Woods 2007[44]	1. Urinary mercury, by treatment group • Mean creatinine-adjusted mcg/g (95% CI), baseline, years 1-7 of follow up ○ Amalgam, 1.8 (NR), NR ○ Composite, 1.9 (NR), NR ○ **Statistically significant difference (t-test) between groups in all years of follow up *P* < 0.01** • Mean, unadjusted mcg/L (95% CI), baseline, yr2 of follow up, years 1 and 3-7 of follow up ○ Amalgam, 1.5 (NR), 3.2 (NR), NR ○ Composite, NR(NR), NR(NR), NR ○ **Statistically significant difference (t-test) between groups in years 2-6 of follow up *P* < 0.001** ○ **No significant difference (t-test) between groups in year 7 of follow up *P* = 0.07** 2. Urinary mercury, by treatment group and sex • Mean, unadjusted mcg/L (95% CI) ○ Amalgam ▪ Female, year 2 of follow up *P* = 3.5 (NR); all other years reported as "about 3" (p. 1529) (95% CI NR) ▪ Male, all years of follow up reported as "<3" (p. 1529) (95% CI NR) ▪ **Significantly higher levels of urinary mercury in females in all years of follow up (*P* < 0.05), except year 3 (*P* = NS)** ○ Composite ▪ Female, NR (NR) ▪ Male, NR (NR) ▪ **No significant difference between females and males in any year of follow up *P* = NS**	"Treatment groups were comparable in baseline urinary mercury concentration (~1.5 mcg/L). Mean urinary mercury concentrations in the amalgam group increased to a peak of ~3.2 mcg/L at year 2 and then declined to baseline levels by year 7 of follow-up…. Girls excrete significantly higher concentrations of mercury in the urine than boys with comparable treatment, suggesting possible sex-related differences in mercury handling and susceptibility to mercury toxicity."
Bellinger 2008[38]	1. Psychosocial function, • CBCL mean (SD) change in scores, baseline to 5 yrs	"In summary, in NECAT, a randomized trial, the psychosocial status of children

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ Composite Scores (i.e., subscales combined) ▪ Competence • Amalgam, 0.8 (0.6) • Composite, −0.9 (0.6) • **No significant difference (ANCOVA) between groups *P* = 0.13** ▪ Internalizing • Amalgam, −3.8 (0.6) • Composite, −2.1 (0.6) • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.03** ▪ Externalizing • Amalgam, −1.8 (0.6) • Composite, −1.5 (0.8) • **No significant difference (ANCOVA) between groups *P* = 0.06** ▪ Total problem behaviors • Amalgam, −3.3 (0.7) • Composite, −2.1 (0.7) • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.007** ○ Competence Subscale Scores ▪ Activities • Amalgam, 1.7 (0.7) • Composite, 0.2 (0.6) • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.03** ▪ Social adaptation • Amalgam, −0.8 (0.7) • Composite, −2.0 (0.7) • **No significant difference (ANCOVA) between groups *P* = 0.11** ▪ School • Amalgam, 0.8 (0.7) • Composite, 1.3 (0.7) • **No significant difference (ANCOVA) between groups *P* = 0.52**	in the dental amalgam group was not worse and, in some respects, was better than that of children in the non-amalgam group."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ Behaviour Subscale Scores ▪ Withdrawn • Amalgam, −1.0 (0.4) • Composite, −0.3 (0.4) • **No significant difference (ANCOVA) between groups *P* = 0.16** ▪ Somatic complaints • Amalgam, −0.1 (0.6) • Composite, 0.0 (0.5) • **No significant difference (ANCOVA) between groups *P* = 0.88** ▪ Anxious/depressed • Amalgam, −0.8 (0.4) • Composite, 0.1 (0.4) • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.04** ▪ Social problems • Amalgam, −0.4 (0.5) • Composite, −0.2 (0.5) • **No significant difference (ANCOVA) between groups *P* = 0.72** ▪ Thought problems • Amalgam, −1.5 (0.5) • Composite, −1.1 (0.5) • **No significant difference (ANCOVA) between groups *P* = 0.44** ▪ Attention problems • Amalgam, −1.1 (0.4) • Composite, −0.6 (0.4) • **No significant difference (ANCOVA) between groups *P* = 0.26** ▪ Delinquent behaviors • Amalgam, −1.8 (0.6) • Composite, −0.2 (0.5) • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.002** ▪ Aggression • Amalgam, −0.3 (0.4)	

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	• Composite, 0.2 (0.4) • **No significant difference (ANCOVA) between groups *P* = 0.28** • BASC-SR ○ Global scores (i.e., subscales combined) at 5yrs, mean (SD) ▪ School maladjustment • Amalgam, 50.8 (0.7) • Composite, 50.4 (0.7) • **No significant difference (ANCOVA) between groups *P* = 0.29** ▪ Clinical maladjustment • Amalgam, 44.0 (0.6) • Composite, 45.7 (0.6) • **No significant difference (ANCOVA) between groups *P* = 0.08** ▪ Personal adjustment • Amalgam, 53.3 (0.6) • Composite, 51.3 (0.6) • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.005** ▪ Emotional symptoms index • Amalgam, 44.6 ± 0.6 • Composite, 46.3 ± 0.6 • **Significant difference (ANCOVA) between groups favours amalgam *P* = 0.05** ○ Subscale scores NR	
Lauterbach 2008[43]	1. Presence of neurological hard signs (NHS), n/pts evaluated (%) • Baseline ○ Amalgam, 9/253 (3.6) ○ Composite, 6/253 (2.4) ○ **No significant difference (Fisher's exact) between groups *P* = 0.60** • Year 1 of follow-up ○ Amalgam, 10/235 (4.3) ○ Composite, 11/231 (4.8) ○ **No significant difference (Fisher's exact) between groups *P* = 0.83** • Year 2 of follow-up ○ Amalgam, 12/230 (5.2)	"This study's results show clearly that children exposed to elemental mercury from dental amalgam, a substance potentially toxic to the nervous system, do not differ from similar children without amalgam exposure in terms of gross and fine neurological development, as assessed in routine clinical neurological examinations. Thus, these data indicate the absence of a generalized negative effect on children's

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ Composite, 12/222 (5.4) ○ **No significant difference (Fisher's exact) between groups *P* > 0.99** • Year 3 of follow-up ○ Amalgam, 4/197 (2.0) ○ Composite, 7/185 (3.8) ○ **No significant difference (Fisher's exact) between groups *P* = 0.37** • Year 4 of follow-up ○ Amalgam, 7/197 (3.6) ○ Composite, 4/193 (2.1) ○ **No significant difference (Fisher's exact) between groups *P* = 0.54** • Year 5 of follow-up ○ Amalgam, 12/194 (6.2) ○ Composite, 15/200 (7.5) ○ **No significant difference (Fisher's exact) between groups *P* = 0.69** • Year 6 of follow-up ○ Amalgam, 13/146 (8.9) ○ Composite, 11/144 (7.6) ○ **No significant difference (Fisher's exact) between groups *P* = 0.83** • Year 7 of follow-up ○ Amalgam, 11/136 (8.1) ○ Composite, 20/142 (14.1) ○ **No significant difference (Fisher's exact) between groups *P* = 0.13** 2. Presence of tremor, n/pts evaluated (%) • Year 1 of follow-up ○ Amalgam, 2/100 (2.0) ○ Composite, 1/105 (1.0) ○ **No significant difference (Fisher's exact) between groups *P* = 0.61** • Year 2 of follow-up ○ Amalgam, 4/230 (1.7) ○ Composite, 2/222 (0.9) ○ **No significant difference (Fisher's exact) between groups *P* = 0.69** • Year 3 of follow-up ○ Amalgam, 0/197 (0.0) ○ Composite, 1/185 (0.5) ○ **No significant difference (Fisher's exact) between groups *P* = 0.48** • Year 4 of follow-up ○ Amalgam, 0/197 (0.0)	nervous system functions stemming from the presence of dental amalgam, and while we cannot rule out potential adverse reactions in individual children, we found no indications of any."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ Composite, 0/193 (0.0) ○ **No significant difference (Fisher's exact) between groups *P* > 0.99** • Year 5 of follow-up ○ Amalgam, 5/194 (2.6) ○ Composite, 5/200 (2.5) ○ **No significant difference (Fisher's exact) between groups *P* > 0.99** • Year 6 of follow-up ○ Amalgam, 5/146 (3.4) ○ Composite, 5/144 (3.5) ○ **No significant difference (Fisher's exact) between groups *P* > 0.99** • Year 7 of follow-up ○ Amalgam, 6/135 (4.4) ○ Composite, 7/142 (4.9) ○ **No significant difference (Fisher's exact) between groups *P* > 0.99** 3. Presence of NSS, n/pts evaluated (%) • Year 2 of follow-up ○ Amalgam, 155/228 (68.0) ○ Composite, 174/222 (78.4) ○ **Significant difference (Fisher's exact) between groups favours amalgam *P* = 0.02** • Year 3 of follow-up ○ Amalgam, 139/197 (70.6) ○ Composite, 130/185 (70.3) ○ **No significant difference (Fisher's exact) between groups *P* > 0.99** • Year 4 of follow-up ○ Amalgam, 119/197 (60.4) ○ Composite, 113/193 (58.5) ○ **No significant difference (Fisher's exact) between groups *P* = 0.76** • Year 5 of follow-up ○ Amalgam, 97/197 (50.0) ○ Composite, 113/200 (56.5) ○ **No significant difference (Fisher's exact) between groups *P* = 0.23** • Year 6 of follow-up ○ Amalgam, 65/146 (44.5) ○ Composite, 59/144 (41.0) ○ **No significant difference (Fisher's exact) between groups *P* = 0.56** • Year 7 of follow-up	

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ Amalgam, 43/135 (31.9) ○ Composite, 53/142 (37.3) ○ **No significant difference (Fisher's exact) between groups *P* = 0.38** 4. NSS score (0-3), (n) mean±SD • Year 3 of follow-up ○ Amalgam, (175) 1.61±1.68 ○ Composite, (168) 1.79±1.65 ○ **No significant difference (t-test) between groups *P* = 0.33** • Year 4 of follow-up ○ Amalgam, (197) 1.20±1.48 ○ Composite, (193) 1.20±1.32 ○ **No significant difference (t-test) between groups *P* = 0.97** • Year 5 of follow-up ○ Amalgam, (194) 0.99±1.52 ○ Composite, (200) 1.16±1.59 ○ **No significant difference (t-test) between groups *P* = 0.31** • Year 6 of follow-up ○ Amalgam, (146) 0.85±1.31 ○ Composite, (144) 0.75±1.25 ○ **No significant difference (t-test) between groups *P* = 0.51** • Year 7 of follow-up ○ Amalgam, (135) 0.46±0.81 ○ Composite, (142) 0.57±0.94 ○ **No significant difference (t-test) between groups *P* = 0.29**	
Shenker 2008[40]	1. Amalgam exposure • Cumulative average number of surfaces restored with amalgam over the study's duration ○ Amalgam, 10.6 ○ Composite, 0 • Mean number of surfaces restored with amalgam at 5yr follow up ○ Amalgam, 4.2 ○ Composite, NR 2. Urinary elemental mercury levels • Mean mcg/g creatinine, yrs 3, 4, 5 ○ Amalgam, 0.89, 0.81, 0.85 ○ Composite, 0.64, 0.50, 0.68 ○ **Statistically significant difference between groups (method NR) in yr 4**	"This study confirms that treatment of children with dental amalgams leads to increased, albeit low level, exposure to mercury. In this exploratory analysis of immune function, amalgam exposure did not cause overt immune deficits, although small transient effects were observed 5–7 days post restoration... These findings suggest that immunotoxic effects of amalgam restorations in children need not be a concern when choosing this restorative dental material."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	***P* = 0.03** ○ **No significant difference between groups (method NR) in yr 3 *P* = 0.07 and yr 5 *P* = 0.20** 3. Immune function changes from baseline at 5-7 days; 6; 12; and 60 months post-intervention • Total WBC, (n) mean change±NR ○ Amalgam, (23) −0±3.6; (24) 0.6±3.5; (17) 1.2±5.8; (20) −1.0±4.0 ○ Composite, (24) 0.4±7.2; (29) 0.7±3.8; (21) −0.4±3.6; (23) −1.7±5.5 ○ **No significant difference (ANCOVA) between groups *P* = NR** • T-cell function ○ %CD25+ (PHA), (n) mean change±NR ▪ Amalgam, (23) −6.0±25.3; (24) 2.0±31.4; (17) 13.8±18.6; (20) 14.8±16.3 ▪ Composite, (24) 1.3±28.1; (28) 4.7±36.3; (21) 13.6±30.7; (23) 14.0±24.4 ▪ **No significant difference (ANCOVA) between groups *P* = NR** ○ %CD69+ (PHA), (n) mean change±NR ▪ Amalgam, (23) −6.5±23.6; (24) −1.5±26.3; (17) 5.7±9.6; (20) 0.9±17.0 ▪ Composite, (24) 4.2±20.8; (28) 4.5±20.6; (21) 5.5±28.4; (23) 4.0±17.9 ▪ **No significant difference (ANCOVA) between groups *P* = NR** ○ Cell cycle distribution at 72hrs ▪ Findings NR • B-cell function ○ %CD23+ (PHA), (n) mean change±NR ▪ Amalgam, (23) 2.5±12.5; (24) 9.8±25.7; (17) −1.3±27.7; (20) −3.3±26.9 ▪ Composite, (24) 1.5±21.7; (28) 13.0±28.4; (21) 3.8±30.7; (23) 10.9±23.5 ▪ **No significant difference (ANCOVA) between groups *P* = NR** ○ %CD69+ (PWM), (n) mean change±NR ▪ Amalgam, (23) −5.2±16.8; (24) −0.4±24.9; (17) −5.9±22.3; (20) −8.4±24.9 ▪ Composite, (24) −2.2±21.6; (28) 5.2±21.9; (21) −1.3±26.9; (23) 1.8±14.1 ▪ **No significant difference (ANCOVA) between groups *P* = NR** • Monocyte function ○ % Eth+(PMA), (n) mean change±NR ▪ Amalgam, (23) −7.8±26.4; (24) −6.2±19.9; (17) −30.7±22.7; (20) 6.3±21.1 ▪ Composite, (24) 5.7±19.6; (27) −4.9±30.1; (21) −18.4±26.1; (22) 3.1±26.8 ○ % Rho+(PMA), (n) mean change±NR ▪ Amalgam, (23) −8.4±30.2; (24) −5.6±27.7; (17) −22±20.8; (20) 7.8±24.5	

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	▪ Composite, (24) 0.4±29.2; (27) −2.1±29.7; (21) −15.3±26.7; (22) 8.8±28.7 • **No significant difference (ANCOVA) between groups *P* = NR** • Neutrophil function, (n) mean change±NR ○ % Eth+(PMA) ▪ Amalgam, (23) −6.5±20.4; (24) −8.3±24.9; (17) −14.5±23.6; (20) 2.3±8.1 ▪ Composite, (24) 3.1±21.1; (28) −9.8±34.6; (21) −13.4±36.6; (23) 6.1±19.6 ○ % Rho+(PMA) ▪ Amalgam, (23) −8.0±19.5; (24) −5.0±29.7; (17) −7.3±31.1; (20) 1.8±13.0 ▪ Composite, (24) 7.2±24.5; (28) −0.5±26.3; (21) −2.0±25.4; (23) 9.3±25.4 • **No significant difference (ANCOVA) between groups *P* = NR**	
Maserejian 2012[37]	(i) BMI-for-age Z-score, 5-year difference (SE) • Females ○ Amalgam, 0.21 (0.07) ○ Composite, 0.36 (0.06) ○ **No significant difference (linear, mixed-effects model) between groups *P* = 0.49** • Males ○ Amalgam, 0.25 (0.07) ○ Composite, 0.13 (0.08) ○ **No significant difference (linear, mixed-effects model) between treatment groups *P* = 0.36** (ii) Body fat %, 5-year difference (SE) • Females, ○ Amalgam, 7.7 (0.8) ○ Composite, 8.8 (0.7) ○ **No significant difference (linear, mixed-effects model) between treatment groups *P* = 0.95** • Males ○ Amalgam, 5.7 (0.9) ○ Composite, 4.9 (0.9) ○ **No significant difference (linear, mixed-effects model) between treatment groups *P* = 0.49** (iii) Height in cm, 5-year difference (SE) • Females, ○ Amalgam, 31.2 (0.5) ○ Composite, 30.7 (0.5)	"Overall, there were no significant differences in physical development over 5 years in children treated with composites or amalgam. Additional studies examining these restoration materials in relation to age at menarche are warranted."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	○ **No significant difference (linear, mixed-effects model) between treatment groups *P* = 0.51** • Males, ○ Amalgam, 33.5 (0.6) ○ Composite, 34.4 (0.6) ○ **No significant difference (linear, mixed-effects model) between treatment groups *P* = 0.56** (iv) Menarche • Females who reached menarche during 5yr study follow up, n (%) ○ Amalgam, 34 (66.7) ○ Composite, 30 (48.4) ○ **Females in the amalgam group significantly more likely to reach menarche HR = 0.57 (95% CI) *P* = 0.03** • Age at first menarche, mean yrs (SD) ○ Amalgam, 12.3 (1.0) ○ Composite, 12.5 (1.1) ○ **No significant difference (proportional hazards model) between treatment groups *P* = 0.48**	
Barregard, 2008[42]	1. Renal biomarker values, median (n) range • **Albumin** ○ Amalgam, year 3: 6.8 (135) < DL-773; year 5: 6.0 (193) < DL-771 ○ Composite, year 3: 7.9 (148) < DL-208; year 5: 6.5 (186) < DL-687 ○ **No significant difference between groups (ANCOVA) *P* = 0.46** • **A1M** ○ Amalgam, year 3: < DL (135) < DL-29; year 5: < DL (193) < DL-29 ○ Composite, year 3: < DL (148) < DL-21; year 5: < DL (186) < DL-29 ○ **No significant difference between groups (ANCOVA) *P* = 0.79** • **γ-GT** ○ Amalgam, baseline: 19.5 (238) 2.1-66; year 5: 39.3 (204) 3.6–125 ○ Composite, baseline: 17.4 (223) 2.0-62; year 5: 40.2 (198) 2.6–143 ○ **No significant difference between groups (ANCOVA) *P* = 0.86** • **NAG** ○ Amalgam, year 3: 1.4 (135) < DL–4.7; year 5: 1.2 (193) < DL–3.7 ○ Composite, year 3: 1.4 (148) < DL–4.8; year 5: 1.2 (186) < DL–7.8 ○ **No significant difference between groups (ANCOVA) *P* = 0.95**	"In summary, the present randomized clinical trial showed no effect of amalgam on renal tubular function. There was, however, an increased prevalence of [albumin] in children treated with dental amalgam. This may reflect a causal association or it may be a chance finding. This issue should be examined further."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	2. Prevalence of 'high' renal biomarker values (as defined), n/sample (%) • **Albumin** ('high' >30 mg/g creatinine) ○ Amalgam, year 3: 18/135 (13) year 5: 30/193 (16) ○ Composite, year 3: 15/148 (9.5); year 5: 18/186 (9.7) ○ **No significant difference (logistic regression) between groups *P* = 0.07** ○ **No significant difference (crude OR, yrs 3-5) OR = 1.6, 95% CI 0.98–2.5 *P* = 0.06** ○ **Significant difference (repeat-measures logistic regression, yr 3 or yr 5) between groups favours composite resin, OR = 1.8, 95% CI 1.1–2.9 *P* = 0.03** • **A1M** ('high' >10.5 mg/g creatinine) ○ Amalgam, year 3: 5/135 (3.7); year 5: 5/193 (2.6) ○ Composite, year 3: 13/148 (8.8); year 5: 3/186 (1.6) ○ **No significant difference (logistic regression) between groups *P* = 0.89** • **γ-GT** ('high' >71.9 U/g creatinine) ○ Amalgam, year 1: 2/186 (1.1); year 5: 20/204 (9.8) ○ Composite, year 1: 2/182 (1.1); year 5: 20/198 (10) ○ **No significant difference (logistic regression) between groups *P* = 0.85** • **NAG** ('high' >3.1 U/g creatinine) ○ Amalgam, year 3: 5/135 (3.7); year 5: 5/193 (2.6) ○ Composite, year 3: 8/148 (5.4); year 5: 8/186 (4.3) ○ **No significant difference (logistic regression) between groups *P* = 0.59**	
Woods 2008[41]	1. Urinary mercury • Baseline urinary mercury, mean mcg/g creatinine ○ Amalgam, 1.8 ○ Composite, 1.9 2. Renal function • Log-transformed, creatinine-adjusted mcg/g GST-α, (n) mean±SD ○ Amalgam, age 9yrs (56) 1.85±1.15, age 10yrs (109) 2.14±1.17, age 11yrs (175) 1.98±1.17, age 12yrs (218) 1.82±1.11, age 13yrs (217) 1.94±0.96, age 14yrs (209) 1.70±0.99, age 15yrs (194) 1.58±0.95, age 16yrs (171) 1.65±0.96, age 17yrs (125) 1.68±0.94, age 18yrs (54) 1.60±0.90 ○ Composite, age 9yrs (59) 2.21±0.99 age 10yrs (135) 2.00±1.11, age 11yrs (192) 2.07±1.10, age 12yrs (208) 1.89±0.97, age 13yrs (212) 1.80±1.05, age 14yrs (208) 1.69±0.96, age 15yrs (205) 1.60±1.00,	"In conclusion, we observed no significant effects of dental amalgam mercury on measures of renal tubular or glomerular functional integrity during a prolonged course of dental amalgam treatment in children and adolescents from 9 to 18 years of age. These findings are relevant within the context of children's health risk assessment as relates to the safety of mercury exposure from dental amalgam on kidney function."

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	age 16yrs (159) 1.51±0.95, age 17yrs (97) 1.49±0.91, age 18yrs (54) 1.50±0.84 ○ **No significant difference between treatment groups** ▪ unadjusted (1.05, 95% CI 0.95-1.17) *P* = 0.308 ▪ adjusted (1.05, 95% CI 0.94-1.17) *P* = 0.405 • Log-transformed, creatinine-adjusted mcg/g GST-π, (n) mean±SD ○ Amalgam, age 9yrs (55) 0.68±1.12, age 10yrs (104) 0.59±1.16, age 11yrs (171) 0.61±1.05, age 12yrs (165) 0.87±1.19, age 13yrs (152) 1.25±1.04, age 14yrs (89) 1.38±1.03, age 15yrs (73) 1.73±1.03, age 16yrs (65) 2.25±0.91, age 17yrs (99) 2.25±0.93, age 18yrs (61) 2.33 0.99 ○ Composite, age 9yrs (51) 0.86±1.06, age 10yrs (117) 0.62±1.01, age 11yrs (167) 0.71±1.11, age 12yrs (164) 0.91±1.14, age 13yrs (139) 1.10±1.22, age 14yrs (90) 1.24±1.11, age 15yrs (92) 1.77±1.10, age 16yrs (69) 2.15±0.97, age 17yrs (80) 2.02±0.91, age 18yrs (60) 2.21 0.90 ○ **No significant difference between treatment groups** ▪ unadjusted (1.08, 95% CI 0.96-1.20) *P* = 0.203 ▪ adjusted (1.11, 95% CI 0.98-1.26) *P* = 0.091 • Log-transformed, creatinine-adjusted mg/g albumin, (n) mean±SD ○ Amalgam, age 9yrs (44) 2.43±0.74, 10yrs (106) 2.18±0.99, 11yrs (158) 2.06±1.09, 12yrs (228) 2.17±1.08, 13yrs (229) 2.33±0.93, 14yrs (214) 2.35±0.94, 15yrs (204) 2.36±1.01, 16yrs (172) 2.20±1.01, 17yrs (126) 2.18±1.06, 18yrs (60) 2.21 1.09 ○ Composite, age 9yrs (53) 2.46±0.91, 10yrs (125) 2.28 1.13, 11yrs (171) 2.23±1.24, 12yrs (222) 2.23±0.97, 13yrs (218) 2.42±1.09, 14yrs (219) 2.44±1.03, 15yrs (219) 2.31±1.01, 16yrs (158) 2.33±1.09, 17yrs (104) 2.13±0.87, age 18yrs (60) 2.16±1.11 ○ **No significant difference between treatment groups** ▪ unadjusted (0.92, 95% CI 0.82-1.04) *P* = 0.179	

Study	Quantitative Findings or Narrative Summary	Authors' Conclusions
	▪ adjusted (0.91, 95% CI 0.78-1.07) *P* = 0.274 • Creatinine-adjusted urinary albumin > 30 mg/gm creatinine, OR (amalgam: composite) *P*-values (Wald test) ○ Age 9yrs 0.7 *P* = 0.72, 10yrs 0.3 *P* = 0.52 11yrs 0.8 *P* = 0.69, 12yrs 0.8 *P* = 0.67, 13yrs 0.8 *P* = 0.70, 14yrs 0.9 *P* = 0.78, 15yrs 0.5 *P* = 0.52, 16yrs 0.8 *P* = 0.72, 17yrs 1.5 *P* = 0.66, 18yrs 1.0 *P* = 0.83 ○ **No significant difference between treatment groups at any follow up time point**	
Woods 2009[39]	1. Baseline urinary mercury, mean mcg/g creatinine • Amalgam, 1.8 • Composite, 1.9 2. Urinary porphyrins, all children • "Slightly elevated" (p. 893) levels (values NR) of penta-, precopro-, and coproporphyrins in the amalgam group ***P* = NR** • **No significant differences between treatment groups in uro- (8-carboxyl), hepta- (7-carboxyl), or hexa- (6-carboxyl) porphyrins *P* = NR** 3. Urinary porphyrins, 8 and 9 year old children only • Increased levels (values NR) of penta-, precopro-, and coproporphyrins in the amalgam group • **No significant differences between treatment groups *P* = NS**	"In conclusion, the present findings describe incipient increases in the urinary concentrations of porphyrins previously defined in association with Hg body burden, in children and adolescents with dental amalgam Hg exposure. These findings attest to the sensitivity of porphyrin changes in relation to Hg exposure and may be useful within the context of risk assessment for low-level Hg exposure in children."
Sensitivity		
Kemaloglu 2016[36]	1. VAS scores, baseline, 6, 12, 36mos • Raw scores NR • **No significant difference (Wilcoxon signed rank test) between groups at baseline, 6 and 12 mos *P* > 0.05** • **Significant difference (Wilcoxon signed rank test) between groups at 36mos favours composite resin *P* < 0.05**	"In postoperative sensitivity criteria, resin composites presented lower sensitivity levels than amalgams after 3 years. Within the limitations of this study, it can be concluded that resin composite can be an alternative for bonded amalgam restorations and can be used with utmost assurance even in large size cavities."

CI = confidence interval; DL = detection limit; HR = hazard ratio; NR = not reported; NS = not significant; OR = odds ratio; PHA = phytohemagglutinin; PMA = phorbol myristate acetate; PWM = pokeweed mitogen; SD = standard deviation; SE = standard error; yrs = years

Appendix 10: Supplemental health economics tables and figures

Table 24: Previously published models identified by the literature search

ECONOMIC MODELS/ANALYSES						
Author	**Year**	**Country**	**Treatment compared**	**Type of analysis/ Type of model**	**Time horizon**	**Comments**
Beazoglou[52]	2007	USA	Amalgam and composite resin	Financial impact of amalgam ban	15 years	Using 1992-2004 trends in usage of composite resin and amalgam in dental claims to project future usage and estimate the impact of a sudden amalgam ban
Elhennawy[53]	2017	Germany	Tooth removal & orthodontic alignment vs resin composite restoration vs crown for the management of molars with severe molar-incisor hypomineralization	Cost-effectiveness/ Markov	Lifetime in a 6 year old child	Transition probabilities (e.g., replacement of composite restoration, crown, implant) from literature Costs from German public tariffs
Kanzow[54]	2016	Germany	Repairing vs replacing composite or amalgam restorations in 4-surface defective permanent molars	Cost-effectiveness/ Markov	Lifetime in a 40 year old individual	Proportion of different re-treatments based on large practice-based study Costs from German public tariffs Assumptions of interest: • Complete replacement did not add additional surface to the restoration but was only possible twice before crown placement • 50% of extracted teeth were replaced by implant-supported single crown
Kelly[55]	2004	Australia	Indirect restorations vs class II cusp-overlay amalgam vs class IV multisurface resin composite restorations	Cost-effectiveness using chart review data	15 years in 40 year old adults	15-year survival of amalgam and composite resin restorations No information on subsequent restorations
Maryniuk[56]	1988	USA	Amalgam vs crown for the replacement of failed amalgam restoration	Cost-effectiveness/ Decision-tree	Lifetime in a 30 year old adult	Probabilities to progress to crown or have root canal treatment are not based on existing evidence Costs of restorations based on tariffs
Schwendicke[57]	2014	Germany	Non-invasive (prevention and fluoride) vs micro-invasive	Cost-effectiveness/ Markov	20 year old adult	Details on transition probabilities Costs from public German tariffs

ECONOMIC MODELS/ANALYSES						
Author	**Year**	**Country**	**Treatment compared**	**Type of analysis/ Type of model**	**Time horizon**	**Comments**
			(resin infiltration) vs invasive (composite restoration) of proximal posterior lesion			
Schwendicke[58]	2015	Germany	Immediate restoration without secondary root canal treatment vs secondary root canal treatment followed by restoration in a defective root canal restored tooth	Cost-effectiveness/ Markov	Lifetime in 50 year old patient	
Sjogren[59]	2002	Sweden	Class II molar restorations	Cost per year of function	Restoration failure time	Reporting a cost per year of function Combining longevity from literature to Swedish tariffs
Tobi[60]	1999	The Netherlands	Composite resin vs amalgam for the replacement of amalgam Class II restorations	Costs and effectiveness alongside a clinical study	5 years	Treatment times from a study by Kreulen are used to calculate costs (dentist office perspective)
Warren E[61]	2016	Australia	Caries Management System vs no intervention	Patient-level simulation	Lifetime	Age distribution similar to Australian population One Markov model per tooth (8 molars) Using combined anterior and posterior tooth data from a study. States: no disease, enamel caries, dentine caries, filling, repeat filling, root canal, crown extraction, bridge, Implant and death. Baseline values from Australian Institute of Health and Welfare. Subsequent events are assumed to increase by 1 when they enter the filling, repeat filling and tooth extraction states. Validation with 7-year study data shows the model under predicts the number of restorations. (note: suppl tables not available online)
Warren E[62]	2010	Australia	Caries Management System vs no intervention	Patient-level simulation	Lifetime	Same as above but with 3-year data only.

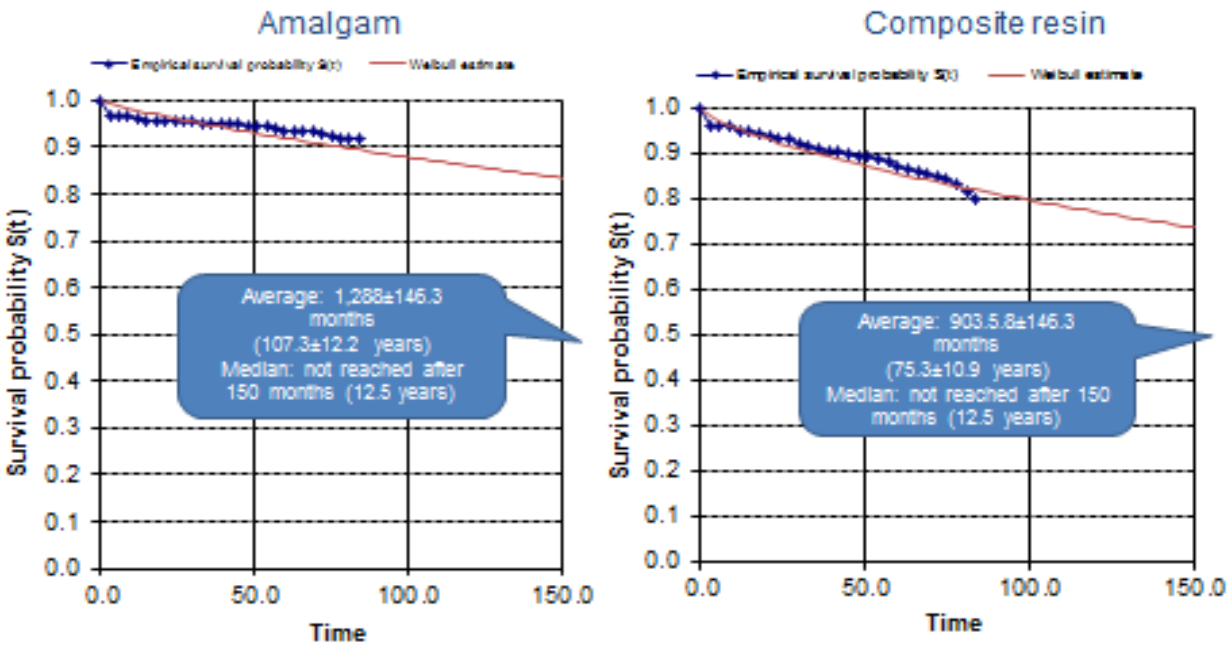
Table 25: Cost-consequence model inputs

Parameter	Consequence				Base case value	Values for PSA	Values for scenario/sensitivity analysis	Source
	1	2	3	4				
Time-to-failure (amalgam)	X	X			132.5104 months	SD: 16.2416 (normal distribution)	Smallest difference scenario: 131.0994 months Largest difference scenario: 133.9214 months	NECAT figure on time-to-failure for permanent posterior teeth digitalized and extrapolated to identified average and SD.[67]
Time-to-failure (composite resin)	X	X			95.7682 months	SD: 6.5337 (normal distribution)	Smallest difference scenario: 96.2349 months Largest difference scenario: 95.3015 months	NECAT figure on time-to-failure for permanent posterior teeth digitalized and extrapolated to identified average and SD.[67]
Costs of dental restorations –privately paid (amalgam)	X	X			$172.18	99.7% CI: $133.60 to $207.00 (normal distribution of log transformed values)	All surfaces scenario: $187.30(99.7%CI: $85.30, $294.00)	Average of dental fees for 2- and 3-surface restoration of the premolars and molars (i.e., codes: 21212, 21213, 21222, 21223 for amalgam and 23312, 23313, 23322, 23323 for composite resin) from all public and private fee lists obtained[81]
Cost of dental restorations – privately paid (composite resin)	X	X			$220.82	99.7% CI: $177.00 to $282.00 (normal distribution of log transformed values)	All surfaces scenario: $241.66 (99.7%CI: $128.70, $401.00)	
Costs of dental restorations –publicly paid (amalgam)	X	X			$131.12	99.7% CI: $56.23 to $180.95 (normal distribution of log transformed values)	All surfaces scenario: $144.18(99.7%CI: $25.68, $268.24)	
Cost of dental restorations – publicly paid (composite resin)	X	X			$182.90	99.7% CI: $88.30 to $275.40 (normal distribution of log transformed values)	All surfaces scenario: $198.82 (99.7%CI: $51.34, $370.53)	
Relative proportion of posterior tooth restorations	X	X					21221 and 23311: 0.09798 21212 and 23312: 0.16661 21213 and 23313: 0.12086 21214 and 23314: 0.04888 21215 and 23315: 0.01194 21221 and 23321: 0.14641 21222 and 23322: 0.19239 21223 and 23323: 0.13157 21224 and 23324: 0.00647 21225 and 23325: 0.01819	(Mrs. Mary Bartlett, Social Development – Health Services Program, Fredericton, NB: personal communication, 2018 Jan 18)
Age at first restoration (amalgam)		X			7.9 years	SD: 1.3 (normal distribution)		NECAT[67]

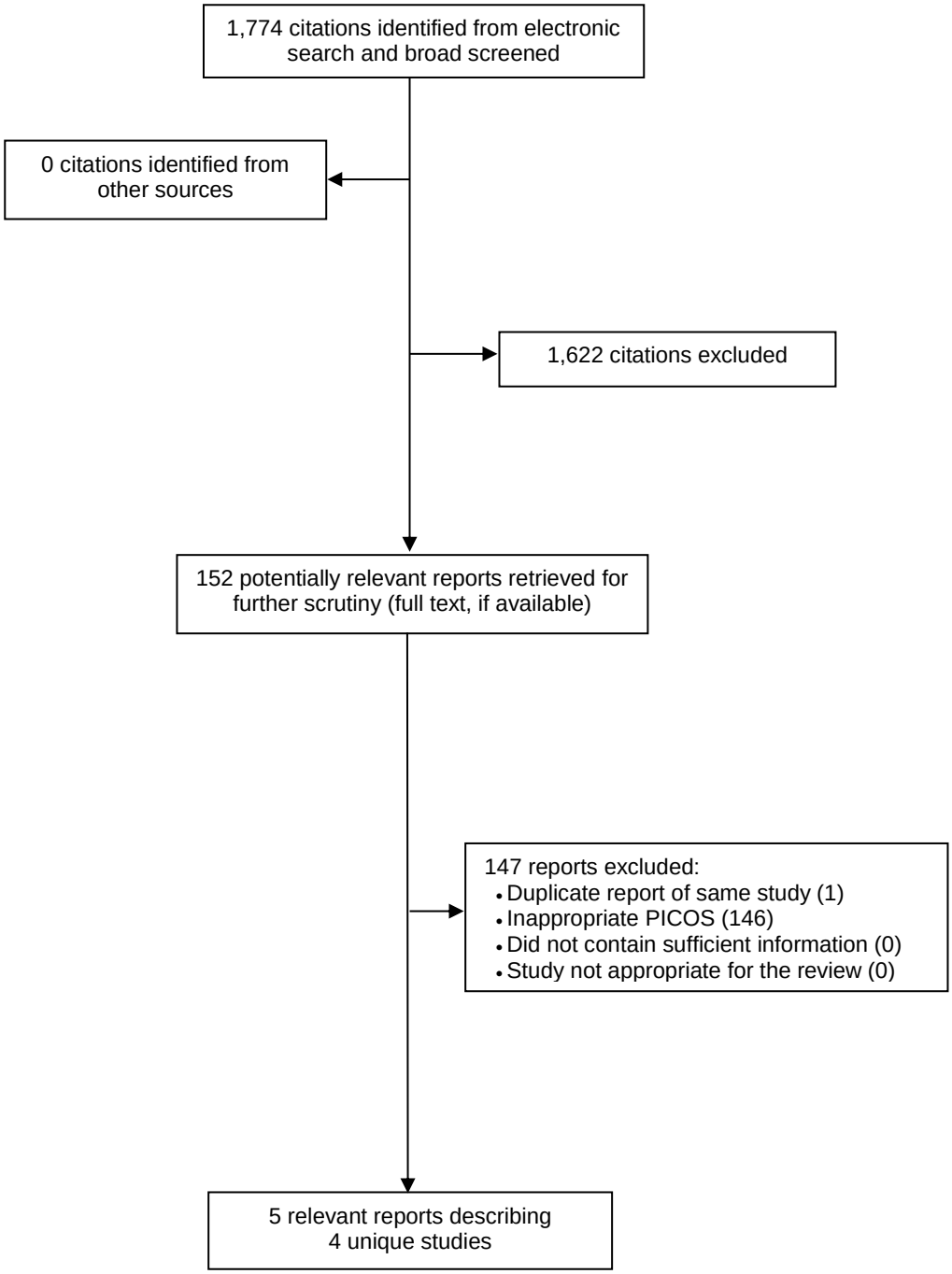
Parameter	Consequence				Base case value	Values for PSA	Values for scenario/sensitivity analysis	Source
	1	2	3	4				
Age at first restoration (composite resin)		X			7.9 years	SD: 1.4 (normal distribution)		NECAT[67]
Proportion of individuals covered by a public program	X	X			0.055	SE: 0.0072 (normal distribution)		Oral Health Survey 2009[66]
Probability of death at restoration failure		X			As per Canadian life tables			Statistics Canada[69]
Cost of a crown (privately paid)		X				99.7%CI: $167.00, $1,300 (normal distribution of log transformed values)	Crown scenario: $623.58	Average of the following procedure codes: 22311, 22320, 27113, 27121, 27201, 27215, 27301, 27413 from all public and private fee lists obtained [81]
Cost of a crown (publicly paid)		X				99.7%CI: $96.26, $801.06 (normal distribution of log transformed values)	Crown scenario: $543.77	
Cost of a tooth extraction (privately paid)		X				99.7%CI: $120.00, $139.00 (normal distribution of log transformed values)	Crown & extraction scenarios: $130.79	Average of procedure code 71101 from all public and private fee lists obtained [81]
Cost of a tooth extraction (publicly paid)		X				99.7%CI: $38.51, $130.30 (normal distribution of log transformed values)	Crown & extraction scenarios: $98.62	
Probability of crown failure at 10 years		X					Crown scenario: 0.7795	Kolker JL et al[73]
Time to extraction		X				99.7%CI: 1.20, 9.20 (normal distribution of log transformed values)	Crown scenario: 6.90 years	Kolker JL et al[73]
Consumer price index		X	X		Multiple values	Not applicable	Not applicable	Bank of Canada[86]
Amalgam separator acquisition and installation costs			X		$2,000	Not applicable	Not applicable	(S.E.: expert opinion, 2017 Aug)
Amalgam separator maintenance and recycling annual costs			X		$2,200	Not applicable	Not applicable	(S.E.: expert opinion, 2017 Aug)
Useful time of amalgam separator			X		5 years	Not applicable	Not applicable	Statistics Canada [244]
Number of dentist using amalgam in Canada			X		13,982	Not applicable	Not applicable	Environmental Impact section

Parameter	Consequence				Base case value	Values for PSA	Values for scenario/sensitivity analysis	Source
	1	2	3	4				
Average number of dentist per clinic			X		2.1	Not applicable	Not applicable	CDA 2010 report[83]
2-surface amalgam restoration procedure time				X	24.3 minutes	95%CI: 11.3, 46.5	Lower limit of time scenario: 11.3 Higher limit of time scenario: 46.5	Advokaat et al [79]
3-surface amalgam restoration procedure time				X	30.0 minutes	95%CI: 15.6, 59.0	Lower limit of time scenario: 15.6 Upper limit of time scenario: 59.0	Advokaat et al [79]
Premolar 2-surface restoration multiplier				X	0.90	Not applicable	Not applicable	Advokaat et al [79]
Premolar 3-surface restoration multiplier				X	0.89	Not applicable	Not applicable	Advokaat et al [79]
Molar 2-surface restoration multiplier				X	1.13	Not applicable	Not applicable	Advokaat et al [79]
Molar 3-surface restoration multiplier				X	1.14	Not applicable	Not applicable	Advokaat et al [79]
Composite resin procedure time multiplier				X	1.15	99.7%CI: 1.05, 1.30 (normal distribution of log transformed values)	Lower limit of multiplier scenario: 1.05 Upper limit of multiplier scenario: 1.30	Assumption
Average hourly wage				X	$26.96	99.7%CI: $13.19, $46.38 (normal distribution of log transformed values)	Lower limit of wage scenario: $13.19 Upper limit of wage scenario: $46.38	Statistics Canada [84]
Proportion of Canadians in labour force				X	0.6567	SE: 0.0015 (beta distribution)		Statistics Canada[85]

Figure 6: Curve fitting and extrapolation of time to restoration failure from the Casa Pia study data



Appendix 11: Study Selection Flow Diagram — Patients' Perspectives and Experiences Review



Appendix 12: List of Excluded Studies and Reasons for Exclusion —Patients' Perspectives and Experiences Review

Table 26: Excluded studies based on full text read (n=147)

Authors	Title	Published Year	Reason for exclusion
Maciel,R.; Salvador,D.; Azoubel,K.; Redivivo,R.; Maciel,C.; da,Franca C.; Amerongen,E.; Colares,V.	The opinion of children and their parents about four different types of dental restorations in a public health service in Brazil	2017	Exclusion reason: Wrong outcomes;
Faraj,B.M.; Mohammad,H.M.; Mohammad,K.M.	The changes in dentists' perception and patient's acceptance on amalgam restoration in Kurdistan-Iraq: a questionnaire-based cross-sectional study	2015	Exclusion reason: Wrong study design;
Levey,E.; Carson,S.; Innes,N.	Patients give meaning to changes in health complaints before, during and after the replacement of amalgam restorations	2015	Exclusion reason: Commentary on study by Sjursen;
Mortazavi,G.; Mortazavi,S.M.	Increased mercury release from dental amalgam restorations after exposure to electromagnetic fields as a potential hazard for hypersensitive people and pregnant women	2015	Exclusion reason: Wrong study design;
Mallineni,S.K.; Nuvvula,S.; Matinlinna,J.P.; Yiu,C.K.; King,N.M.	Biocompatibility of various dental materials in contemporary dentistry: a narrative insight	2013	Exclusion reason: Wrong study design;
Tillberg,A.; Stenberg,B.; Berglund,A.	Reactions to resin-based dental materials in patients--type, time to onset, duration, and consequence of the reaction	2009	Exclusion reason: Wrong study design;
Dye,B.A.; Schober,S.E.; Dillon,C.F.; Jones,R.L.; Fryar,C.; McDowell,M.; Sinks,T.H.	Urinary mercury concentrations associated with dental restorations in adult women aged 16-49 years: United States, 1999-2000	2005	Exclusion reason: Wrong outcomes;
Naumann,J.	Mercury as the suspected agent. Alzheimer disease due amalgam dental fillings? (interview by Dr. Judith Neumaier)	2005	Exclusion reason: editorial;
Westman,J.F.	Creating a supportive environment. An update from the Minnesota Dental Association's Committee on Environment, Wellness and Safety	2003	Exclusion reason: Wrong study design;
Casetta,I.; Invernizzi,M.; Granieri,E.	Multiple sclerosis and dental amalgam: case-control study in Ferrara, Italy	2001	Exclusion reason: Wrong study design;
McGrother,C.W.; Dugmore,C.; Phillips,M.J.; Raymond,N.T.; Garrick,P.; Baird,W.O.	Multiple sclerosis, dental caries and fillings: a case-control study	1999	Exclusion reason: Wrong study design;
Bergdahl,J.; Tillberg,A.; Stenman,E.	Odontologic survey of referred patients with symptoms allegedly caused by electricity or visual display units	1998	Exclusion reason: Wrong study design;
Bangsi,D.; Ghadirian,P.; Ducic,S.; Morisset,R.; Ciccocioppo,S.; McMullen,E.; Krewski,D.	Dental amalgam and multiple sclerosis: a case-control study in Montreal, Canada	1998	Exclusion reason: Wrong study design;
Chong,B.S.; Pitt Ford,T.R.; Kariyawasam,S.P.	Short-term tissue response to potential root-end filling materials in infected root canals	1997	Exclusion reason: Wrong outcomes;
Thomson,W.M.; Stewart,J.F.; Carter,K.D.; Spencer,A.J.	The Australian public's perception of mercury risk from dental restorations	1997	Exclusion reason: Wrong study design;

Authors	Title	Published Year	Reason for exclusion
Koppel,C.; Fahron,G.	Toxicological and neuropsychological findings in patients presenting to an environmental toxicology service	1995	Exclusion reason: Wrong study design;
Lorscheider,F.L.; Vimy,M.J.; Summers,A.O.	Mercury exposure from "silver" tooth fillings: emerging evidence questions a traditional dental paradigm	1995	Exclusion reason: Wrong study design;
Schuurs,A.H.; Eijkman,M.A.; Hoogstraten,J.	Patient views on dental amalgam. An exploratory questionnaire	1994	Exclusion reason: Wrong study design
Osborne,J.W.	The amalgam story continues. Interview by Stephen Hancocks	1994	Exclusion reason: editorial;
Drasch,G.; Schupp,I.; Hofl,H.; Reinke,R.; Roider,G.	Mercury burden of human fetal and infant tissues	1994	Exclusion reason: Wrong outcomes;
Williams,P.; Kasloff,Z.	Mercury (and the debate goes on)	1991	Exclusion reason: editorial;
Yontchev,E.; Hedegard,B.; Carlsson,G.E.	Reported symptoms, diseases, and medication of patients with orofacial discomfort complaints	1986	Exclusion reason: Wrong outcomes;
Khowassah,M.A.; Denehy,G.E.	A qualitative study of the interface between different dental amalgams and retentive pins	1973	Exclusion reason: Wrong outcomes;
Lygre,G.B.; Gjerdet,N.R.; Bjrkman,L.	A follow-up study of patients with subjective symptoms related to dental materials	2005	Exclusion reason: Wrong study design;
Furhoff,A.; Tomson,Y.; Ilie,M.; BÇ¾gedahl-Strindlund,M.; Larsson,K.S.; Sandborgh-Englund,G.; Torstenson,B.; Wretlind,K.	A multidisciplinary clinical study of patients suffering from illness associated with release of mercury from dental restorations: Medical and odontological aspects	1998	Exclusion reason: Wrong study design;
Rothwell,J.A.; Boyd,P.J.	Amalgam dental fillings and hearing loss	2008	Exclusion reason: Wrong study design;
Lye,Ellen; Legrand,Melissa; Clarke,Janine; Probert,Adam	Blood total mercury concentrations in the canadian population: canadian health measures survey cycle 1, 2007-2009	2013	Exclusion reason: Wrong outcomes;
Sjursen,T.T.; Lygre,G.B.; Dalen,K.; Helland,V.; LGreid,T.; Svahn,J.; Lundekvam,B.F.; Bj-Rkman,L.	Changes in health complaints after removal of amalgam fillings	2011	Exclusion reason: Wrong study design;
Maserejian,Nancy N.; Trachtenberg,Felicia L.; Wheaton,Olivia Brown; Calafat,Antonia M.; Ranganathan,Gayatri; Hae-Young,Kim; Hauser,Russ	Changes in urinary bisphenol A concentrations associated with placement of dental composite restorations in children and adolescents	2016	Exclusion reason: Wrong study design;
Leistevuo,J.; Leistevuo,T.; Helenius,H.; Pyy,L.; -sterblad,M.; Huovinen,P.; Tenovuo,J.	Dental amalgam fillings and the amount of organic mercury in human saliva	2001	Exclusion reason: Wrong outcomes;
Wahl,Michael J.	Critical appraisal: dental amalgam update--part II: biological effects	2013	Exclusion reason: Wrong study design;
Naimi-Akbar,Aron; Svedberg,Pia; Alexanderson,Kristina; Carlstedt-Duke,Bodil; Ekstrand,Jan; Englund,Gunilla Sandborgh	Health-related quality of life and symptoms in patients with experiences of health problems related to dental restorative materials	2013	Exclusion reason: Wrong study design;
Shenker,B.J.; Maserejian,N.N.; Zhang,A.; McKinlay,S.	Immune function effects of dental amalgam in children: a randomized clinical trial	2008	Exclusion reason: Wrong study design;

Authors	Title	Published Year	Reason for exclusion
Browning,W.D.	Incidence and severity of postoperative pain following routine placement of amalgam restorations	1999	Exclusion reason: Wrong outcomes
Bedir Findik,Rahime; Celik,Huseyin Tugrul; Ersoy,Ali Ozgur; Tasci,Yasemin; Moraloglu,Ozlem; Karakaya,Jale	Mercury concentration in maternal serum, cord blood, and placenta in patients with amalgam dental fillings: effects on fetal biometric measurements	2016	Exclusion reason: Wrong outcomes;
Factor-Litvak,P.; Hasselgren,G.; Jacobs,D.; Begg,M.; Kline,J.; Geier,J.; Mervish,N.; Schoenholtz,S.; Graziano,J.	Mercury derived from dental amalgams and neuropsychologic function	2003	Exclusion reason: Wrong outcomes;
Moss,J.	Mercury revisited - part II: does body burden tell the whole story?	2008	Exclusion reason: Wrong study design;
Crisp,R.J.; Burke,F.J.T.	One-year clinical evaluation of compomer restorations placed in general practice	2000	Exclusion reason: Wrong study design;
Ishitobi,H.; Stern,S.; Thurston,S.W.; Zareba,G.; Langdon,M.; Gelein,R.; Weiss,B.	Organic and inorganic mercury in neonatal rat brain after prenatal exposure to methylmercury and mercury vapor	2010	Exclusion reason: Wrong patient population;
Weidenhammer,W.; Bornschein,S.; Zilker,T.; Eyer,F.; Melchart,D.; Hausteiner,C.	Predictors of treatment outcomes after removal of amalgam fillings: associations between subjective symptoms, psychometric variables and mercury levels	2010	Exclusion reason: Wrong study design;
Espelid,I.; Cairns,J.; Askildsen,J.E.; Qvist,V.; Gaarden,T.; Tveit,A.B.	Preferences over dental restorative materials among young patients and dental professionals	2006	Exclusion reason: Wrong study design;
Mackert,J.R.,Jr.	Randomized controlled trial demonstrates that exposure to mercury from dental amalgam does not adversely affect neurological development in children	2010	Exclusion reason: Wrong study design;
Browning,W.D.; Johnson,W.W.; Gregory,P.N.	Reduction of postoperative pain: a double-blind, randomized clinical trial	1997	Exclusion reason: Wrong outcomes;
Barregard,L.; Trachtenberg,F.; McKinlay,S.	Renal effects of dental amalgam in children: the New England Children's Amalgam Trial	2008	Exclusion reason: Wrong study design;
Lygre,G.B.; Gjerdet,N.R.; Grnningster,A.G.; Bjrkman,L.	Reporting on adverse reactions to dental materials -- intraoral observations at a clinical follow-up	2003	Exclusion reason: Wrong study design;
Kidd,R.F.	Results of dental amalgam removal and mercury detoxification using DMPS and neural therapy	2000	Exclusion reason: Wrong outcomes;
Sundstrm,A.; Bergdahl,J.; Nyberg,L.; Bergdahl,M.; Nilsson,L.	Stressful negative life events and amalgam-related complaints	2011	Exclusion reason: Wrong study design;
Keller,S.; Martin,C.G.; Evensen,C.T.; Mitton,C.R.	The development and testing of a survey instrument for benchmarking dental plan performance: using insured patients' experiences as a gauge of dental care quality	2009	Exclusion reason: Wrong study design;
Stejskal,V.D.; Danersund,A.; Lindvall,A.; Hudecek,R.; Nordman,V.; Yaqob,A.; Mayer,W.; Bieger,W.; Lindh,U.	Metal-specific lymphocytes: biomarkers of sensitivity in man	1999	Exclusion reason: Wrong outcomes;
Aljawad,A.; Rees,J.S.	Retrospective study of the survival and patient satisfaction with composite Dahl restorations in the management of localised anterior tooth wear	2016	Exclusion reason: Wrong intervention;
Pawar,R.R.; Mattigatti,S.S.; Mahaparale,R.R.; Kamble,A.P.	Lichenoid reaction associated with silver amalgam restoration in a Bombay blood group patient: A case report	2016	Exclusion reason: duplicate;

Authors	Title	Published Year	Reason for exclusion
Syed,M.; Chopra,R.; Sachdev,V.	Allergic reactions to dental materials-a systematic review	2015	Exclusion reason: Wrong study design;
Rathore,M.; Singh,A.; Pant,V.A.	The dental amalgam toxicity fear: a myth or actuality	2012	Exclusion reason: Wrong study design;
Burke,F.J.; Crisp,R.J.	A practice-based assessment of patients' knowledge of dental materials	2015	Exclusion reason: Wrong outcomes;
Lynch,M.; Ryan,A.; Galvin,S.; Flint,S.; Healy,C.M.; O'Rourke,N.; Lynch,K.; Rogers,S.; Collins,P.	Patch testing in oral lichenoid lesions of uncertain etiology	2015	Exclusion reason: Wrong outcomes;
Wilson,J.	Amalgam as a filling material for the older person--a personal opinion	2014	Exclusion reason: editorial;
Berkowitz,G.; Spielman,H.; Matthews,A.; Vena,D.; Craig,R.; Curro,F.; Thompson,V.	Postoperative hypersensitivity and its relationship to preparation variables in Class I resin-based composite restorations: findings from the practitioners engaged in applied research and learning (PEARL) Network. Part 1	2013	Exclusion reason: Wrong study design;
Parizi,J.L.; Nai,G.A.	Amalgam tattoo: a cause of sinusitis?	2010	Exclusion reason: Wrong outcomes;
Stahlnacke,K.; Soderfeldt,B.	Factors related to persons with health problems attributed to dental filling materials--part one in a triangular study on 65 and 75 years old Swedes	2012	Exclusion reason: Wrong study design;
Capozza,L.E.; Bimstein,E.	Preferences of parents of children with autism spectrum disorders concerning oral health and dental treatment	2012	Exclusion reason: Wrong study design;
da Silva,G.R.; Roscoe,M.G.; Ribeiro,C.P.; da Mota,A.S.; Martins,L.R.; Soares,C.J.	Impact of rehabilitation with metal-ceramic restorations on oral health-related quality of life	2012	Exclusion reason: Wrong study design;
Bamise,C.T.; Oginni,A.O.; Adedigba,M.A.; Olagundoye,O.O.	Perception of patients with amalgam fillings about toxicity of mercury in dental amalgam	2012	Exclusion reason: Wrong study design;
Eyeson,J.; House,I.; Yang,Y.H.; Warnakulasuriya,K.A.	Relationship between mercury levels in blood and urine and complaints of chronic mercury toxicity from amalgam restorations	2010	Exclusion reason: Wrong study design;
Roberts,H.W.; Charlton,D.G.	The release of mercury from amalgam restorations and its health effects: a review	2009	Exclusion reason: Wrong study design;
Zimmerman,J.A.; Feigal,R.J.; Till,M.J.; Hodges,J.S.	Parental attitudes on restorative materials as factors influencing current use in pediatric dentistry	2009	Exclusion reason: Wrong study design;
Kovarik,R.E.	Restoration of posterior teeth in clinical practice: evidence base for choosing amalgam versus composite	2009	Exclusion reason: Wrong study design;
Mutter,J.; Naumann,J.; Guethlin,C.	Comments on the article "the toxicology of mercury and its chemical compounds" by Clarkson and Magos (2006)	2007	Exclusion reason: editorial;
Schedle,A.; Ortengren,U.; Eidler,N.; Gabauer,M.; Hensten,A.	Do adverse effects of dental materials exist? What are the consequences, and how can they be diagnosed and treated?	2007	Exclusion reason: Wrong study design;
Lygre,G.B.; Helland,V.; Gjerdet,N.R.; Bjorkman,L.	Health complaints related to dental filling materials	2007	Exclusion reason: Wrong study design;
Fan,P.L.; Meyer,D.M.	FDI report on adverse reactions to resin-based materials	2007	Exclusion reason: Wrong study design;
Fishman,R.; Guelmann,M.; Bimstein,E.	Children's selection of posterior restorative materials	2006	Exclusion reason: Wrong study design;

Authors	Title	Published Year	Reason for exclusion
Bjorkman,L.; Weiner,J.; Gjerdet,N.R.	Improvement of health after replacement of amalgam fillings?	2005	Exclusion reason: Wrong study design;
Lygre,G.B.; Gjerdet,N.R.; Bjorkman,L.	Patients' choice of dental treatment following examination at a specialty unit for adverse reactions to dental materials	2004	Exclusion reason: Wrong study design;
Segura-Egea,J.J.; Bullon-Fernandez,P.	Lichenoid reaction associated to amalgam restoration	2004	Exclusion reason: Wrong study design;
Scott,A.; Egner,W.; Gawkrodger,D.J.; Hatton,P.V.; Sherriff,M.; van,Noort R.; Yeoman,C.; Grummitt,J.	The national survey of adverse reactions to dental materials in the UK: a preliminary study by the UK Adverse Reactions Reporting Project	2004	Exclusion reason: Wrong study design;
Dalen,K.; Lygre,G.B.; Klove,H.; Gjerdet,N.R.	Personality variables in patients with self-reported reactions to dental amalgam	2003	Exclusion reason: Wrong outcomes;
ADA Council on Scientific Affairs	Direct and indirect restorative materials	2003	Exclusion reason: Wrong study design;
Peretz,B.; Ram,D.	Restorative material for children's teeth: preferences of parents and children	2002	Exclusion reason: Wrong study design;
Lindh,U.; Hudecek,R.; Danersund,A.; Eriksson,S.; Lindvall,A.	Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health	2002	Exclusion reason: Wrong study design;
Gilmore,H.W.	Treat patients' concerns as well as their oral health	2001	Exclusion reason: Wrong study design;
Dlugokinski,M.; Browning,W.D.	Informed consent: direct posterior composite versus amalgam	2001	Exclusion reason: Wrong study design;
Evens,C.C.; Martin,M.D.; Woods,J.S.; Soares,H.L.; Bernardo,M.; Leitao,J.; Simmonds,P.L.; Liang,L.; DeRouen,T.	Examination of dietary methylmercury exposure in the Casa Pia Study of the health effects of dental amalgams in children	2001	Exclusion reason: Wrong intervention;
Sterzl,I.; Hrda,P.; Prochazkova,J.; Bartova,J.; Matucha,P.	Reactions to metals in patients with chronic fatigue and autoimmune endocrinopathy	1999	Exclusion reason: Wrong study design;
Melchart,D.; Wuhr,E.; Weidenhammer,W.; Kremers,L.	A multicenter survey of amalgam fillings and subjective complaints in non-selected patients in the dental practice	1998	Exclusion reason: Wrong study design;
Lofqvist,A.	Important to understand and manage reactions of people with problems connected to amalgam and electricity	1998	Exclusion reason: Wrong language;
Laine,J.; Kalimo,K.; Happonen,R.P.	Contact allergy to dental restorative materials in patients with oral lichenoid lesions	1997	Exclusion reason: Wrong study design;
Blomgren,J.; Axell,T.; Sandahl,O.; Jontell,M.	Adverse reactions in the oral mucosa associated with anterior composite restorations	1996	Exclusion reason: Wrong study design;
Henningsson,M.; Sundbom,E.	Defensive characteristics in individuals with amalgam illness as measured by the percept-genetic method Defense Mechanism Test	1996	Exclusion reason: Wrong study design;
Forss,H.; Widstrom,E.	Factors influencing the selection of restorative materials in dental care in Finland	1996	Exclusion reason: Wrong study design;
Alanko,K.; Kanerva,L.; Jolanki,R.; Kannas,L.; Estlander,T.	Oral mucosal diseases investigated by patch testing with a dental screening series	1996	Exclusion reason: Wrong study design;
Ostman,P.O.; Anneroth,G.; Skoglund,A.	Amalgam-associated oral lichenoid reactions. Clinical and histologic changes after removal of amalgam	1996	Exclusion reason: Wrong study design;

Authors	Title	Published Year	Reason for exclusion
	fillings		
Stoz,F.; Aicham,P.; Jovanovic,S.; Steuer,W.; Mayer,R.	Effects of new dental amalgam fillings in pregnancy on Hg concentration in mother and child. With consideration for possible interactions between amalgam and precious metals	1995	Exclusion reason: Wrong study design;
Henriksson,E.; Mattsson,U.; Hakansson,J.	Healing of lichenoid reactions following removal of amalgam. A clinical follow-up	1995	Exclusion reason: Wrong study design;
Bergdahl,J.; Ostman,P.O.; Anneroth,G.; Perris,H.; Skoglund,A.	Psychologic aspects of patients with oral lichenoid reactions	1995	Exclusion reason: Wrong study design;
Eijkman,M.A.; de,Jongh A.	Amalgam. XII. Amalgam removed and patient cured?	1994	Exclusion reason: Wrong study design;
Ostman,P.O.; Anneroth,G.; Skoglund,A.	Oral lichen planus lesions in contact with amalgam fillings: a clinical, histologic, and immunohistochemical study	1994	Exclusion reason: Wrong outcomes;
Blignaut,J.B.; Louw,N.P.	Replacing amalgam fillings with composite inlays--a case report	1993	Exclusion reason: Wrong study design;
Fallowfield,M.G.	'Dental amalgam: a review'	1993	Exclusion reason: Wrong study design;
Anneroth,G.; Ericson,T.; Johansson,I.; Mornstad,H.; Ryberg,M.; Skoglund,A.; Stegmayr,B.	Comprehensive medical examination of a group of patients with alleged adverse effects from dental amalgams	1992	Exclusion reason: Wrong study design;
Chiodo,G.T.; Tolle,S.W.	Can a patient make an irrational choice? The dental amalgam controversy	1992	Exclusion reason: Wrong study design;
Nordlind,K.; Liden,S.	Patch test reactions to metal salts in patients with oral mucosal lesions associated with amalgam restorations	1992	Exclusion reason: Wrong study design;
Holttinen,T.; Murtomaa,H.; Meurman,J.	Expectant mothers opinion on the use of amalgam and the effect of pregnancy on dental health	1991	Exclusion reason: Wrong outcomes;
Skoglund,A.; Egelrud,T.	Hypersensitivity reactions to dental materials in patients with lichenoid oral mucosal lesions and in patients with burning mouth syndrome	1991	Exclusion reason: Wrong study design;
Meurman,J.H.; Porko,C.; Murtomaa,H.	Patients complaining about amalgam-related symptoms suffer more often from illnesses and chronic craniofacial pain than their controls	1990	Exclusion reason: Wrong study design;
Missias,P.	Biocompatibility of dental amalgam	1990	Exclusion reason: Wrong outcomes;
Taskinen,H.; Kinnunen,E.; Riihimaki,V.	A possible case of mercury-related toxicity resulting from the grinding of old amalgam restorations	1989	Exclusion reason: Wrong study design;
Burke,F.J.	Patient acceptance of posterior composite restorations	1989	Exclusion reason: Wrong study design;
Bellinger,D.C.; Trachtenberg,F.; Daniel,D.; Zhang,A.; Tavares,M.A.; McKinlay,S.	A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function. The New England Children's Amalgam Trial	2007	Exclusion reason: Wrong study design;
Moss,J.	A viewpoint on mercury-part III: how does mercury make us sick?	2001	Exclusion reason: Wrong outcomes;
Hiltunen,Neil S.; Lynch,Christopher D.	COMPOSITES AND AMALGAM.	2011	Exclusion reason: Wrong outcomes;
Bellinger,D.C.; Daniel,D.; Trachtenberg,F.; Tavares,M.;	Dental amalgam restorations and children's neuropsychological function: the New England	2007	Exclusion reason: Wrong study design;

Authors	Title	Published Year	Reason for exclusion
McKinlay,S.	Children's Amalgam Trial		
Himmelberger,Linda K.	Justifiable criticism and dental amalgam	2015	Exclusion reason: editorial;
Issa,Y.; Brunton,P.A.; Glenny,A.M.; Duxbury,A.J.	Healing of oral lichenoid lesions after replacing amalgam restorations: a systematic review	2004	Exclusion reason: Wrong study design;
Hibberd,A.R.; Howard,M.A.; Hunnisett,A.G.	Mercury from dental amalgam fillings: studies on oral chelating agents for assessing and reducing mercury burdens in humans	1998	Exclusion reason: Wrong outcomes;
Munro-Hall,G.; Munro-Hall,L.	Mercury-free dentistry -- a passport to better health	1999	Exclusion reason: editorial;
McGovern,V.	Taking a bite out of amalgam concerns?: study shows no renal effects in children	2008	Exclusion reason: Wrong study design;
Aktas,Bora; Basyigit,Sebahat; YÇ¬ksel,Osman; Akkan,Tolga; Atbas,Suna TÇ¬lin; Uzman,Metin; Ylmaz,Bars; Simsek,G.; NazlgÇ¬l,Yasar; AktaY,Bora; BaYyiYit,Sebahat; AtbaY,Suna TÇ¬lin; Ylmaz,BarY; zimYek,G.; NazlgÇ¬l,YaYar	The impact of amalgam dental fillings on the frequency of Helicobacter pylori infection and H. pylori eradication rates in patients treated with concomitant, quadruple, and levofloxacin-based therapies	2015	Exclusion reason: Wrong outcomes;
Bjrkman,L.; Sjursen,T.T.; Dalen,K.; Lygre,G.B.; Berge,T.L.L.; Svahn,J.; Lundekvam,B.F.	Long term changes in health complaints after removal of amalgam restorations	2017	Exclusion reason: Wrong study design;
Paknahad,M.; Mortazavi,S.M.J.; Shahidi,S.; Mortazavi,G.; Haghani,M.	Effect of radiofrequency radiation from Wi-Fi devices on mercury release from amalgam restorations	2016	Exclusion reason: Wrong outcomes;
Sharma,R.; Handa,S.; De,D.; Radotra,B.; Rattan,V.	Role of dental restoration materials in oral mucosal lichenoid lesions	2015	Exclusion reason: Wrong study design;
MÇ¾rell,L.; Tillberg,A.; Widman,L.; Bergdahl,J.; Berglund,A.	Regression of oral lichenoid lesions after replacement of dental restorations	2014	Exclusion reason: Wrong study design;
Naimi-Akbar,A.; Svedberg,P.; Alexanderson,K.; Ekstrand,J.; Sandborgh-Englund,G.	Reliance on social security benefits by Swedish patients with ill-health attributed to dental fillings: A register-based cohort study	2012	Exclusion reason: Wrong outcomes;
Correa,M.B.; Peres,M.A.; Peres,K.G.; Horta,B.L.; Barros,A.D.; Demarco,F.F.	Amalgam or composite resin? Factors influencing the choice of restorative material	2012	Exclusion reason: Wrong study design;
Geier,D.A.; King,P.G.; Sykes,L.K.; Geier,M.R.	A comprehensive review of mercury provoked autism	2008	Exclusion reason: Wrong study design;
Lidmark,A.M.; Wikmans,T.	Are they really sick? A report on persons who are electrosensitive and/or injured by dental material in Sweden	2008	Exclusion reason: Wrong study design;
Hausteiner,C.; Bornschein,S.; Henningsen,P.; Nowak,D.	Psychosomatic aspects of environmentally related syndromes	2008	Exclusion reason: Wrong language;
Melchart,D.; Vogt,S.; Khler,W.; Streng,A.; Weidenhammer,W.; Kremers,L.; Hickel,R.; Felgenhauer,N.; Zilker,T.; WÇ¬hr,E.; Halbach,S.	Treatment of health complaints attributed to amalgam	2008	Exclusion reason: Wrong outcomes;
Hausteiner,C.; Bornschein,S.; Nowak,D.; Henningsen,P.	Psychosomatic aspects of environmentally related illnesses	2007	Exclusion reason: Wrong language;

Authors	Title	Published Year	Reason for exclusion
Lygre,G.B.; Helland,V.; Gjerdet,N.R.; Bjrkman,L.	Health complaints related to dental materials - A followup study	2007	Exclusion reason: Wrong study design;
Frisk,P.; Lindvall,A.; Hudecek,R.; Lindh,U.	Decrease of trace elements in erythrocytes and plasma after removal of dental amalgam and other metal alloys	2006	Exclusion reason: Wrong study design;
Van Noort,R.; Gjerdet,N.R.; Schedle,A.; Bjrkman,L.; Berglund,A.	An overview of the current status of national reporting systems for adverse reactions to dental materials	2004	Exclusion reason: Wrong outcomes;
Vamnes,J.S.; Lygre,G.B.; Grnningsater,A.G.; Gjerdet,N.R.	Four years of clinical experience with an adverse reaction unit for dental biomaterials	2004	Exclusion reason: Wrong study design;
Kao,R.T.; Dault,S.; Pichay,T.	Understanding the mercury reduction issue: the impact of mercury on the environment and human health	2004	Exclusion reason: Wrong outcomes;
Bailer,J.; Staehle,H.J.; Rist,F.	Sick from amalgam fillings? Selective review of findings from multi-disciplinary studies	2003	Exclusion reason: Wrong study design;
Dunsche,A.; KÇ¾stel,I.; Terheyden,H.; Springer,I.N.G.; Christophers,E.; Brasch,J.	Oral lichenoid reactions associated with amalgam: Improvement after amalgam removal	2003	Exclusion reason: Wrong study design;
Gottwald,B.; Kupfer,J.; Traenckner,I.; Ganss,C.; Gieler,U.	Psychological, allergic, and toxicological aspects of patients with amalgam-related complaints	2002	Exclusion reason: Wrong study design;
Bauer,A.; sen-Hinrichs,C.	Evaluation of 916 suspected cases of environmentally related disorders - A Schleswig-Holstein model project of 1995-1999	2002	Exclusion reason: Wrong study design;
Bauer,A.; sen-Hinrichs,C.; Wassermann,O.	Case study of 916 environmentally related disorders during the period 1995-1999 in Schleswig-Holstein	2001	Exclusion reason: Wrong study design;
Bauer,A.; sen-Hinrichs,C.	Environmental pollution--assessment of environmental medicine questionnaires and data in Schleswig-Holstein from 1995-1997	2000	Exclusion reason: Wrong study design;
Lygre,G.B.; Grnningster,A.G.; Gjerdet,N.R.	Mercury and dental amalgam fillings	1998	Exclusion reason: Wrong study design;
Marcusson,J.A.; Jarstrand,C.	Oxidative metabolism of neutrophils in vitro and human mercury intolerance	1998	Exclusion reason: Wrong outcomes;
Langworth,S.	Experiences from the amalgam unit at Huddinge hospital - Somatic and psychosomatic aspects	1997	Exclusion reason: Wrong study design;
Wiltshire,W.A.; Ferreira,M.R.; Ligthelm,A.J.	Allergies to dental materials	1996	Exclusion reason: Wrong study design;
LÇ¬bbe,J.; WÇ¬thrich,B.	Dental amalgam: Allergy and controversy	1996	Exclusion reason: Wrong study design;
Hanson,M.; Pleva,J.	The dental amalgam issue. A review	1991	Exclusion reason: Wrong study design;
Meurman,J.H.; Porko,C.; Murtomaa,H.	Patients complaining about amalgam-related symptoms suffer more often from illnesses and chronic craniofacial pain than their controls	1990	Exclusion reason: Wrong study design;
Bolewska,J.; Reibel,J.	T lymphocytes, Langerhans cells and HLA__DR expression on keratinocytes in oral lesions associated with amalgam restorations	1989	Exclusion reason: Wrong outcomes;

Appendix 13: List of Included Studies — Patients' Perspectives and Experiences Review

Table 27: List of included studies (n=4 studies, 5 papers)

Full Reference
Marell L, Lindgren M, Nyhlin KT, Ahlgren C, Berglund A. "Struggle to obtain redress": women's experiences of living with symptoms attributed to dental restorative materials and/or electromagnetic fields. Int J Qual Stud Health Well-being, **2016**, 11(32820): 1748-2631
Sjursen TT, Binder P, Lygre GB, Helland V, Dalen K, Bjorkman L. Patients' experiences of changes in health complaints before, during, and after removal of dental amalgam. Int J Qual Stud Health Well-being, **2015**, 10(1): 28157
Sjursen TT, Binder P, Lygre GB, Helland V, Dalen K, Bjorkman L How unexplained health complaints were attributed to dental amalgam. Nord Psychol, **2014**, 66(3): 216-229.
Stahlnacke K and Soderfeldt B. An interview study of persons who attribute health problems to dental filling materials--part two in a triangulation study on 65 and 75 years old Swedes. Swed Dent J, **2013**, 37(3): 121-130.
Jones LM. Focus on fillings: a qualitative health study of people medically diagnosed with mercury poisoning, linked to dental amalgam. Acta Neuropsychiatr, **2004**, 16(3): 142-148.

Appendix 14: Characteristics of Included Studies and their Participants — Patients' Perspectives and Experiences Review

Table 28: Characteristics of included studies (n=4 studies, 5 papers)

Author/ Year /Country	Purpose	Methodology/ Method/ Analysis	Participant Details	Author's Conclusion
Marell L, et al., **2016**[97] Sweden	To explore the experiences of illness and encounters with health care professionals among a group of women with symptoms attributed to dental restorative materials and/or electromagnetic fields	Grounded Theory Semi-structured individual interviews Constant comparative method of analysis	N=13 Female n=13 Age range 37-63 years (Mean 49 years) Inclusion criteria a) belief that symptoms were caused by dental restorations and/or electromagnetic fields; (b) no known signs of contact allergic reaction to dental materials	The core category represents the women's fight for approval and arose in the conflict between their experience of developing a severe illness and the doctors' or dentists' rejection of the symptoms as a disease, which made the women feel like malingerers. They experienced better support and confirmation from alternative medicine practitioners. However, the need for sick-leave certificates led to a continuous cycle of visits in the health care system. To avoid conflicting encounters, it is important for caregivers to listen to the patient's explanatory models and experience of illness, even if a medical answer cannot be given.
Sjursen TT, et al., **2015**[96] Norway	To explore how patients experienced and gave meaning to changes in health complaints before, during, and after amalgam removal	Qualitative Semi-structured in-depth interviews Explorative and reflexive thematic analysis	N=12 Women = 7 Men = 5 Age range 45-65 years (Mean 54 years) Participants were interviewed 5 years after they had completed removal of all amalgam fillings	The dental amalgam was certainly important to get rid of, but it is uncertain how important the removal was for the experienced changes in health complaints. Patients were very happy to have had all their amalgam fillings removed, but they did not believe that they could credit all the positive changes to the amalgam removal
Sjursen TT, et al., **2014**[95] Norway	To explore a group of patients' experiences of how they came to attribute their health complaints to dental amalgam	Qualitative Semi-structured in-depth interviews Explorative and reflexive thematic analysis	N=12 Women = 7 Men = 5 Age range 45-65 years (Mean 54 years) Participants were interviewed 5 years after they had completed removal of all amalgam fillings	The presence of unexplained, or partially explained, health complaints compels patients to search for an explanation and thereby also a cure. Participants tried to go about this search for an answer in a logical and to a certain extent also hypothesis-testing manner. Forming such an attribution influenced emotions and initiated actions such as contacting the specialty unit and having amalgam fillings replaced

Author/ Year /Country	Purpose	Methodology/ Method/ Analysis	Participant Details	Author's Conclusion
Stahlnacke K and Soderfeldt B, **2013**[98] Sweden	To understand the experience of living with health problems attributed to dental materials. The study considered the type of problem, general and oral health problems, causes of the problems, their effect on life and the reception by health professionals	Qualitative Semi-structured interviews. Participants interviewed until saturation reached Content analysis	N= 11 Women = 7 Men = 4 Focus group people (n=?) representing "Dental Care Injury Association"	People who attribute their health problems to dental materials have a complex picture of symptoms – somatic, mental and oral – with the first two types dominating. All participants believed that it was the amalgam that was the cause of the problems they experienced, and they all had their amalgam fillings replaced, with varying results. Reception from the healthcare system was generally good with isolated cases of not being treated with respect and consideration
Jones LM. **2004**[99] New Zealand	To document themes from patients' collective, subjective experience; and explore links between illness and dental amalgam	Qualitative 7 focus groups Thematic analysis	N=35 Selected by random, criteria sampling from computerized patient records from one medical practice	Four principal findings of this study: (i) people who linked amalgams and health were not an homogeneous group, but fell into categories differentiated by their sets of symptoms, fiscal resources, and motivation; (ii) there was a major positive relationship between amalgam removal with detoxification, and the recovery of psychological and physical health, although the detoxification process is problematic; (iii) GP or psychiatric consultations created problems in addition to the physical symptoms; and (iv) the placebo effect is not supported as an exclusive explanation for positive health outcomes.

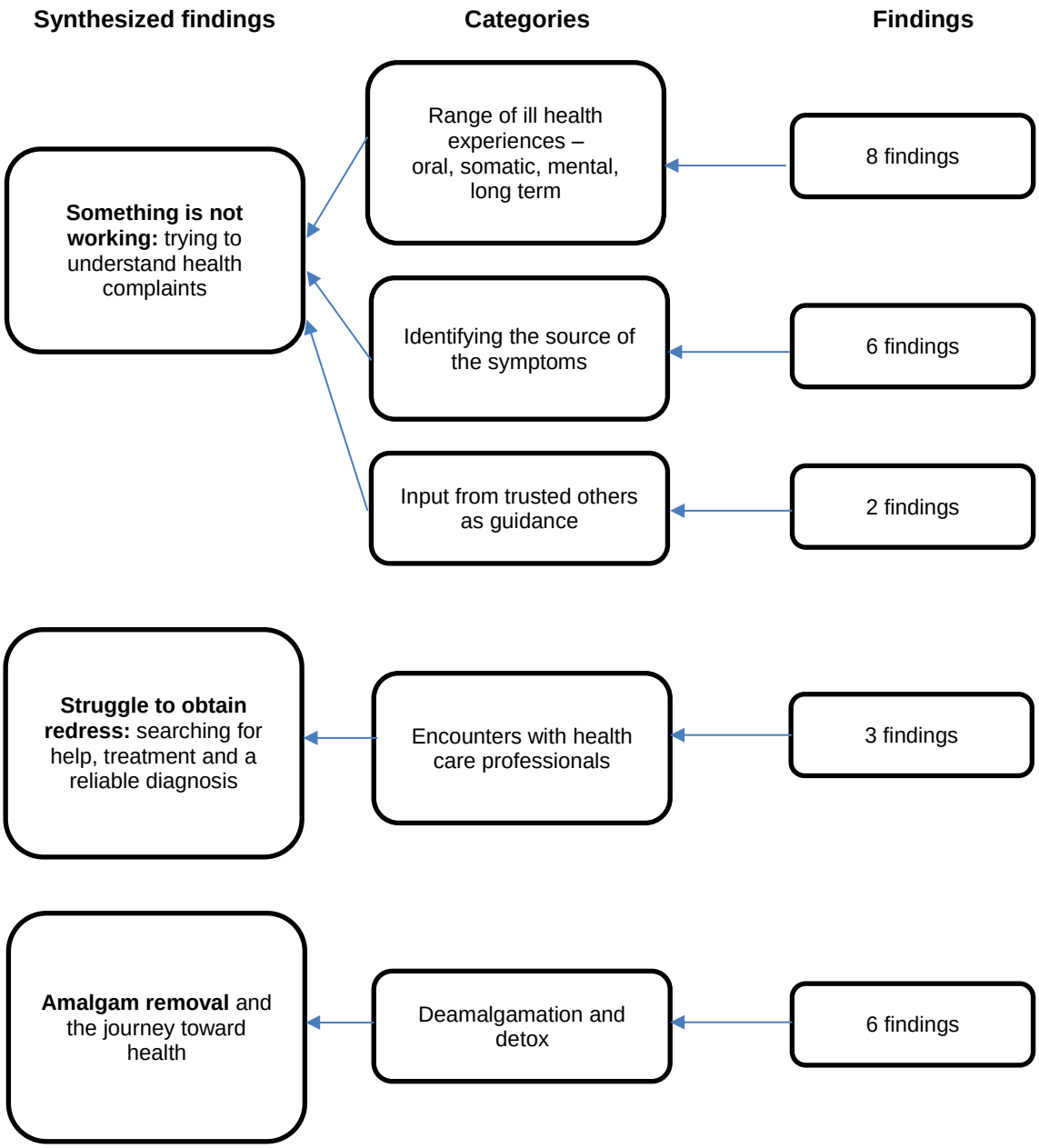
Appendix 15: Quality Assessment of Included Studies — Patients' Perspectives and Experiences Review

Table 29: Assessment of methodological quality (n=4 studies, 5 papers)

Author/ date	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Marell L et al., 2016[97]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/10
Sjursen TT et al., 2015[96] Sjursen TT et al., 2014[95]	N	Y	Y	Y	Y	N	Y	Y	Y	Y	8/10
Stahlnacke K and Soderfeldt B 2013[98]	N	Y	Y	Y	Y	U	Y	Y	Y	Y	8/10
Jones LM 2004[99]	N	Y	Y	Y	Y	N	N	U	Y	Y	6/10
%	0	100	100	100	100	25	75	75	100	100	

Appendix 16: Meta-Synthesis — Patient Preferences Review

Meta-synthesis of the results



Meta-Synthesis Details

Table 30: The relationship of synthesized findings, categories and findings

Synthesized Finding 1 **Something is not working:** trying to understand health complaints
Category 1 Range of ill health experiences – oral, somatic, mental, long term
Long-term problems of varying character caused by dental amalgam: Oral problems, somatic problems, mental problems, long-term problems
Psychological problems of mercury poisoning: i) problems directly attributed to mercury toxicity: memory loss, mood swings, and loss of sensation; ii) problems related to the consequences of having symptoms that were not readily diagnosed namely self-efficacy; the social stigma of being labelled a hypochondriac; the concomitant loss of social support; or being referred for psychological or psychiatric assessment
The four diverse patterns of experience: a) chronic illness experience
The four diverse patterns of experience: b) experiencing minor worries
The four diverse patterns of experience: c) still experiencing chronic illness and still with amalgam
The four diverse patterns of experience: d) single, major illness experience
Feeling puzzled: participants stressed how they were baffled and to some degree overwhelmed by their complaints. Feeling their whole bodily and psychological functioning was influenced by something from the outside, which was described as a feeling of being poisoned
Powerful effect on life, mostly negative, but also some strengthening effects
Category 2 Identifying the source of the symptoms
Feeling a resonance with descriptions of amalgam poisoning
Struggle to obtain redress: Stricken with Illness. The women were convinced that their symptoms were caused by external agents such as dental materials and/or electromagnetic fields. In most cases, they attributed the onset of their symptoms to a dental treatment.
Temporal relationship between dental treatment and episodes of ill health
Feeling puzzled: participants stressed how they were baffled and to some degree overwhelmed by their complaints. Feeling their whole bodily and psychological functioning was influenced by something from the outside, which was described as a feeling of being poisoned
Something is not working: betrayed by the body: the experience of something not working inside their bodies. Some had struggled with health complaints from an early age, whereas others experienced onset of complaints as adults.
You are out there on your own: actively trying to find explanation for their complaints. Several were disappointed by how little the medical profession had to offer when it came to health complaints in the absence of corresponding objective findings
Category 3 Input from trusted others as guidance
A trusted person suggested dental amalgam as an explanation for complaints: sometimes physicians or dentists made the link based on either severe intraoral complaints, such as dry mouth, pain, and a stinging sensation, or repeated episodes of ill health after dental treatment
Picking up anecdotal evidence: anecdotal evidence was important for their first suspicion of dental amalgam as being behind their complaints
Synthesized Finding 2 **Struggle to obtain redress:** searching for help, treatment and a reliable diagnosis
Category 4 Encounters with health care professionals
Struggle to obtain redress: experiences of encounters with doctors and dentists. Although they felt severely ill, they perceived that they were being told they were physically healthy when no somatic pathology could be found.
Good reception from health professionals on the whole; isolated encounters were often the cause of the negative experiences.
You are out there on your own: actively trying to find explanation for complaints. Several were disappointed by how little the medical profession had to offer when it came to health complaints in the absence of corresponding objective findings

Synthesized Finding 3 **Amalgam removal and the journey toward health**
Category 5 Deamalgamation and detox
Change in dental materials in fillings: resulting in anything from no improvement to noticeable improvement. Treatments included odontological treatment, medical treatment and alternative medical treatment
Deamalgamation and detoxification: a variety of experiences following the removal of amalgam
No longer having any amalgam fillings in their teeth associated with being able to cross worry off the list
Not being sure of the importance of amalgam removal: some participants were uncertain of the role of amalgam removal in their change of health status
To accept, to give up, or to continue the search: despite feeling better, as reported by the majority of the participants, none of them had become symptom-free after the amalgam removal
The relief experienced after amalgam removal: despite some uncertainties, the majority of the participants concluded that they were in a much better place in their lives at the time of the interview than they had been before the amalgam removal

Appendix 17: Descriptive Themes and Associated Categories — Patients' Perspectives and Experiences Review

Table 31: Findings and illustrations from each study (n= 5)

Marell L, et al., **"Struggle to obtain redress": Women's experiences of living with symptoms attributed to dental restorative materials and/or electromagnetic fields. Int J Qual Stud Health Well-being, 2016, 11(32820): 1748-2631**		
Findings	**Sub-themes**	**Quotes**
Struggle to obtain redress: Stricken with Illness The women were convinced that their symptoms were caused by external agents such as dental materials and/or electromagnetic fields. In most cases, they attributed the onset of their symptoms to a dental treatment. P 3	Be in mortal danger Multiple symptoms difficult to describe Extrinsic factors invading the body	"When she started her computer, my heart began to beat so fast that I felt I was going to die." p. 3 "I got ache in the head, the neck and the back. My eyes turned red. I could hardly see. I got slime in my throat... and everything came at the same time." p. 4 "When it got worse, I had a hard time at work. I also had an unusual situation at home, but that was still not a contributing factor. In fact, I was ill." p. 4
Struggle to obtain redress: A blot in the protocol Describes the women's experiences of encounters with doctors and dentists when they searched for help, treatment, and a reliable diagnosis. Although they felt severely ill, they perceived that they were being told they were physically healthy when no somatic pathology could be found.	Ill but sound as a bell No acceptable diagnosis	"I remember I was crying when I walked away from the doctor. I figured there was something wrong with me, but nothing was shown, all the investigations and tests showed nothing. They said that I'm healthy even though I feel like this!" p. 4 "You only cause trouble. In fact, you are only a blot in the protocol." P 4 "It is nothing mental, you know. We know that we are right. That is the problem with us." p. 4

Sjursen TT, et al., **Patients' experiences of changes in health complaints before, during, and after removal of dental amalgam. Int J Qual Stud Health Well-being,** 2015**, 10(1): 28157**	
Findings	**Quotes**
Something is not working: betrayed by the body: The starting point for all participants was the experience of something not working inside their bodies. Some had struggled with health complaints from an early age, whereas others experienced onset of complaints as adults.	"I was in so much pain, and I also felt, for a while, that I had such a poor memory (sighs). I cannot say if that was because of stress caused by having to fight the pain, but I did feel ''out of it'' in a way. I really did." p. 4
You are out there on your own: actively trying to find explanation for their complaints. Several were disappointed by how little the medical profession had to offer when it came to health complaints in the absence of corresponding objective findings	"I'm not quite able to sort it out, and the doctors are not very good at helping with these things when they do not find anything specific.... So in a way, you have to sort it out on your own. " p. 4
Not being sure of the importance of amalgam removal: some participants were uncertain of the role of amalgam removal in their change of health status.	"Well, what I think is that I don't really know what (pause). I think that the amalgam removal at least has had an effect on my mouth and the pain I had there. But I (pause) when it comes to the other complaints, I think that it is kind of impossible to know if it is [the amalgam removal] that has made me better or if it is other things. I have tried a lot of different things. I have had different treatments, and I have changed my diet, you know,

Sjursen TT, et al., **Patients' experiences of changes in health complaints before, during, and after removal of dental amalgam. Int J Qual Stud Health Well-being,** 2015**, 10(1): 28157**	
Findings	**Quotes**
	and I have started to take Omega-3 supplements, which is also supposed to be good for the joints, for instance. So, I really have done other things as well, and I really can't say if it is the teeth or if it is the other things or if it is (pause). I find this to be very difficult." p. 5/6
The relief experienced after amalgam removal: Despite some uncertainties, the majority of the participants concluded that they were in a much better place in their lives at the time of the interview than they had been before the amalgam removal.	"This amalgam removal, I do believe it has had an effect, together with all the other things. But I would have to have psychic abilities to know exactly how. As I have told you, there are still periods in which I feel quite poorly and beside myself, but I do feel much better now. I really do." p. 6
No longer having any amalgam fillings in their teeth associated with being able to cross worry off the list	"You know, some (pause). There are many people with the same complaints that I have had who are talking about amalgam and such. So it is possible that if I still had those fillings left, I could have been constantly thinking ''Yes, it really could be those fillings keeping me from feeling well.'' But it is not like that anymore, is it?" p. 6
To accept, to give up, or to continue the search: Despite feeling better, as reported by the majority of the participants, none of them had become symptom-free after the amalgam removal	"Well, in a way I have accepted that I will always have some complaints. I am not like I used to be when I thought that if only I could find the right solution, then I would also get cured. I have kind of given up on that. It is more about finding the best possible way to live with [the complaints]." p.7

Sjursen TT, et al., **How unexplained health complaints were attributed to dental amalgam. Nordic Psychology,** 2014**, 66(3): 216-229**	
Findings	**Quotes**
Feeling puzzled Participants stressed how they were baffled and to some degree overwhelmed by their complaints. Some of these participants described how they felt that their whole bodily and psychological functioning, and not just specific complaints, was influenced by something from the outside. From this, which was described as a feeling of being poisoned, a growing suspicion that dental amalgam could be behind their complaints arose. For others, dental amalgam was not considered a likely cause until it seemed to be the only explanation left after all other options had been exhausted.	"I thought a lot about whether it could be the amalgam. Because, you know, when you're feeling so miserable over time, you'll try everything. You'll try homeopathy and you'll try all sorts (laughs) of other things to figure it out. But when that didn't help, you know, what could it be?" p. 220
Picking up anecdotal evidence: the importance of anecdotal evidence for their first suspicion of dental amalgam as being behind their complaints	"Actually, it was when I was at the rehabilitation center that there was such a huge focus on it, on amalgam. When I came back I told my dentist. He wasn't convinced, but he did contact [the specialty unit] and arranged for me to be examined. So, I've never been absolutely sure about it, if there really has been [a connection]. But it has been a possibility." p. 221
Temporal relationship between dental treatment and episodes of ill health	"Sometimes when I had amalgam fillings replaced I felt absolutely terrible afterwards. Sometimes I even had to stay home from work. (...) I was in pain, I was frightfully tired, and I felt nauseated. (Short pause) It was obnoxious." p. 221

Sjursen TT, et al., **How unexplained health complaints were attributed to dental amalgam. Nordic Psychology,** 2014**, 66(3): 216-229**	
Findings	**Quotes**
A trusted person suggested dental amalgam as an explanation for my complaints: Sometimes physicians or dentists make the link. Participants' dentists suggested the link based on either severe intraoral complaints, such as dry mouth, pain, and a stinging sensation, or repeated episodes of ill health after dental treatment	"Well, it was the dentist who first put me on to the idea, you know. (...) He saw how bad my teeth were and how much pain I was in. (...) I described how I felt at the time, how painful it was and how it burned and ached, you know. " p. 222
Feeling a resonance with descriptions of amalgam poisoning	"And when I was at the specialty unit, I contacted the organization for amalgam poisoning and I read everything I could get my hands on. And then I felt that I had all the complaints (laughs)." p. 223

Stahlnacke K and Soderfeldt B. **An interview study of persons who attribute health problems to dental filling materials--part two in a triangulation study on 65 and 75 years old Swedes. Swedish Dental Journal, 2013, 37(3): 121-130**		
Findings	**Sub-themes**	**Quotes**
Long-term problems of varying character caused by dental amalgam	Oral problems Somatic problems Mental problems Dental materials Long-term problems	Oral - "you feel sore and have so many, many blisters in the mouth, I had, you know" p. 125 Somatic - "that it might have some connection with my teeth that I was often so terribly tired, had pains in my body and felt dizzy and nauseous, had problems roughly like what you think of if you get the flu" p. 125 Mental – "one aspect of it all is that you have a tendency to get terribly depressed" p. 125 Dental – "that there could be a link with the mercury in the amalgam, and so I began to look into this and then I started talking to doctors and dentists and so on, that I was a textbook case of amalgam, eh, mercury poisoning." p. 125 Long term – "so these problems had actually been with me since birth because my mother had huge problems with her teeth and had many amalgam fillings" p. 127
Problems treated mainly with change in dental materials in fillings resulting in anything from no improvement to noticeable improvement	Odontological treatment Medical treatment Alternative medical treatment Varying results of measures taken	"I had all the amalgam removed and my dentist said, you have to get rid of it, you won't get better before that, he said." P. 127 "I can still feel a little now but I've become much better, but it probably took, once all the amalgam was away, it took about two years." p. 127
Powerful effect on life, mostly negative, but also some strengthening effects	Life restricted Life strengthened Not affected	"I felt so bad that I didn't have the strength for any social life" p. 127
Good reception from health professionals on the whole, isolated encounters were often the cause of the negative experiences	Pleased with the reception Displeased with the reception	Pleased - "I got affirmation, she told me a lot about the disease, she told me exactly how to act and, and what, what was important to do" p. 128 Displeased - "met a doctor who didn't listen to me one second but just asked about the divorce and wanted to prescribe nerve tablets and the like for me" p. 128

Jones LM. **Focus on fillings: a qualitative health study of people medically diagnosed with mercury poisoning, linked to dental amalgam. Acta Neuropsychiatrica, 2004, 16(3): 142-148**		
Findings	**Sub-themes**	**Quotes**
Participants did not conform to an anticipated stereotype of a chronically ill person who had shopped around doctors, specialists and alternative health providers, and 'passed through' the medical practice that was the target of the present study, without regaining health p. 145		
Deamalgamation and detoxification: experiences following the removal of amalgam		Majority experienced a full return to health and the activities of daily life. Every group had some participants who mentioned a 'bath' metaphor as a heuristic that explained deamalgamation and detox. Their body was likened to a bath, and dental amalgams likened to a dripping tap. For a person with dental amalgams, the tap was turned on, but with amalgam removal the tap was turned off. In the metaphor, this left 'water in the bath' and it needed to be drained. To detox was to 'pull the plug'. p. 144
Psychological problems of mercury poisoning: First there were the problems directly attributed to mercury toxicity: memory loss, mood swings, and loss of sensation. Second there were the problems related to the consequences of having symptoms that were not readily diagnosed. The issues here were self-efficacy; the social stigma of being labelled a hypochondriac; the concomitant loss of social support; of being referred for psychological or psychiatric assessment		Suicidal thoughts were also referred to during discussion in other groups, including praying to die and dreaming of death. p. 145
The four diverse patterns of Experience	Chronic illness experience	They had 'every test in the book' from blood counts to scans. As the tests never showed anything abnormal, many had been told by doctors that they were 'making it up'… As illness persisted without a medical label or as a psychosomatic condition, these people experienced the negative social stigma of being labelled 'a hypochondriac'. p. 146
	Experiencing minor worries	They had not considered they were ill when they consulted the medical practice, reporting only minor health worries including having a metallic taste in the mouth, tinnitus, and a reduced cognitive efficiency that some referred to as 'brain fog' and others as 'a bad memory'. They also reported having frequent tonsillitis, colds and 'flu'; and noticing a minimal sense of taste and smell. Their decision to have the urine test and to remove amalgam was for future illness prevention, linked for some with 'mercury suppressing the immune system'. p. 145 After deamalgamation and detoxification, these people were surprised both at the return of lost sensation and the speed of recovery. They had not anticipated any immediate benefits but reported the lifting of the 'brain fog', improved smell and taste, an absence of colds and flu symptoms and the end of the metallic taste. This was equated with a major health gain. p. 146
	Still experiencing chronic illness and still with amalgam	Two expressed reservations about the likelihood of amalgam removal being a cure for them….Although there were only a few in this category, there was still a pattern that one needs both a conviction about the efficacy of deamalgamation, and money. p. 146

Jones LM. **Focus on fillings: a qualitative health study of people medically diagnosed with mercury poisoning, linked to dental amalgam. Acta Neuropsychiatrica, 2004, 16(3): 142-148**		
Findings	**Sub-themes**	**Quotes**
	Single, major illness experience.	Several participants reported having an original medical diagnosis of something other than mercury poisoning, which they accepted (i.e. thyroid problems, cancers), but in the course of complying with orthodox treatment for this, they had explored amalgam removal as a way of minimizing a perceived threat to their immune system…When they did decide to try amalgam removal, the results were dramatic (i.e. no surgery or chemotherapy) and their return to health has been enduring, albeit with disease-in-remission diagnoses. p. 146

Appendix 18: Invitation to participate in consultations – Implementation Issues Review

1. Invitation to participate in consultations regarding implementation issues for using dental amalgams and composite resin for dental restorations in Canada

"Dear Dr. X,

I am connecting with you regarding a Health Technology Assessment project comparing dental amalgams and resin composites currently underway at CADTH (Canadian Agency for Drugs and Technologies in Health). Here is the project page with a brief introduction to the project: https://cadth.ca/dental-amalgams-compared-resin-composites

In addition to clinical effectiveness and cost effectiveness, the review will assess evidence on patient experiences, ethical considerations, environmental impact and implementation issues related to using these materials in the treatment of patients. As the Knowledge Mobilization Officer for the project, I will be leading the review of implementation issues as well as any subsequent knowledge mobilization activity of the research results after the completion of the project.

Here are the questions we are trying to address in our implementation issues review:

1. What is the current use of amalgam restorations in Canadian dental practices or programs?
2. What is the current use of composite resin restorations in Canadian dental practices or programs?
3. What factors influence the use of amalgam or composite resin restorations in Canadian dental practices or programs?

We are wondering whether we could connect with you to discuss your perspectives on this issue, other considerations that we should be taking into account when we are looking at this issue as well as your suggestions on others with whom we should connect in order to discuss relevant implementation issues. We are also looking for any literature regarding implementation issues on this subject (our information specialists have already identified a list of articles that we are currently reviewing for relevant information).

Would you please let me know whether you are interested in a brief phone consultation and if so, what is your availability?

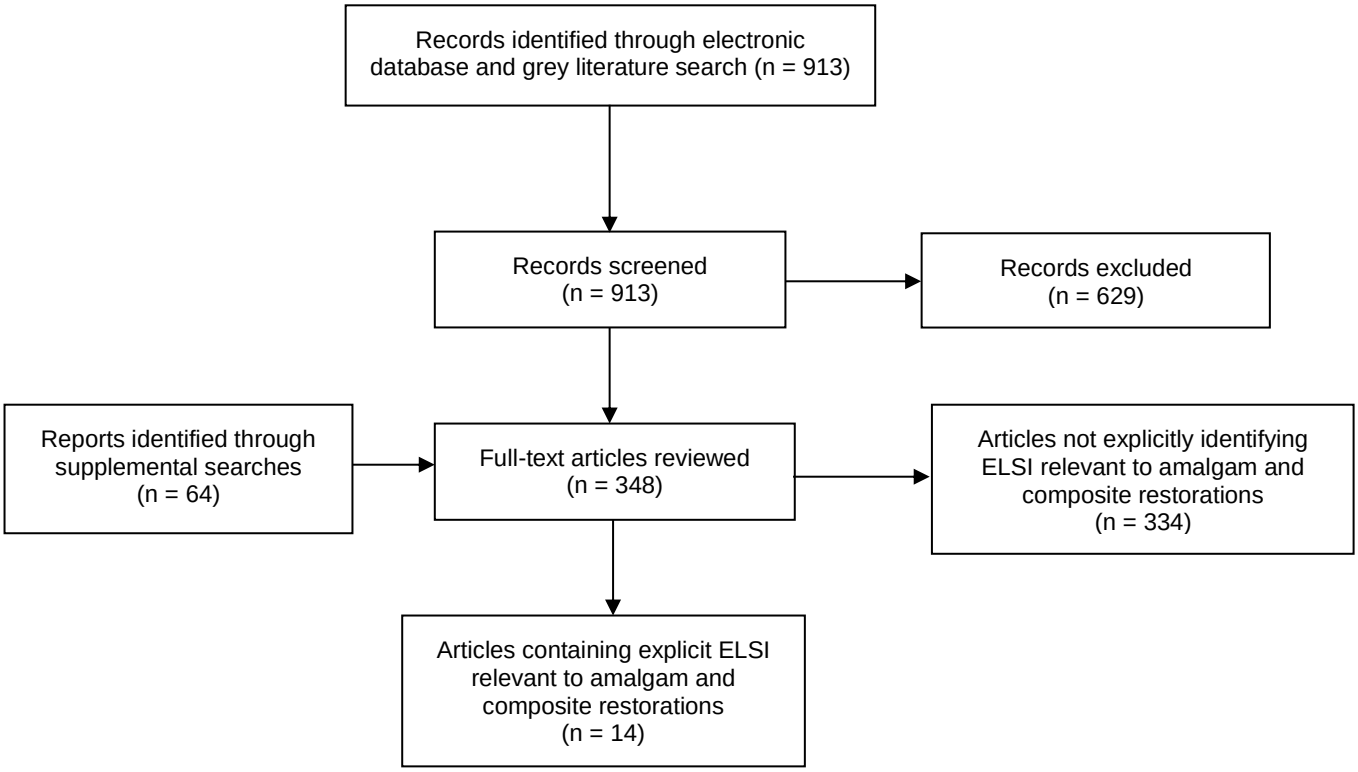
I look forward to hearing from you and hearing your perspectives.

With many thanks in advance."

2. Questions for Consultations with Stakeholders re Implementation Issues

- Do you have any information around the current use of amalgam restorations in Canadian dental practices or programs? Would you know where we can retrieve this type of information/data from?
- Do you have any information around the current use of composite resin restorations in Canadian dental practices or programs? Would you know where we can retrieve this type of information/data from?
- We are interested in understanding the context of use of these materials. According to your experience and knowledge, what factors influence the use of amalgam or composite resin restorations in Canadian dental practices or programs?
    - It would be helpful if you could describe factors that may affect use such as:
        - relevant policies
        - issues related to the dental practice setting
        - cost considerations
        - considerations that relate to the dental providers (e.g., education, training, other)
        - considerations that relate to patients
        - other factors that you are aware of as contributing to the use of these materials in Canadian practices/programs.

Appendix 19: Flow Diagram of Literature Search and Selection Process – Ethics, Legal and Social Issues Review



Appendix 20: Historical Overview of the Amalgam Debate

This appendix provides a brief overview of key historical aspects of the ongoing debate within the dental profession, and in society more generally, about the continuing use of dental amalgam as a restorative material. Understanding and appreciating this history has implications for the kinds of recommendations that may gain moral traction in the current debate, as well as in developing implementation strategies for such recommendations.

Early experimentations with various combinations of mercury (Hg) amalgam were conducted in France and Britain in the early part of the 19th century, and amalgam was eventually introduced to America in the 1830s.[133,143] From the outset, there was debate among dentists as to the safety of mercury amalgams. When the American Society of Dental Surgeons was formed in 1840, its members were required to sign a pledge never to use amalgam because of the known toxicity of mercury. Enforcing that pledge proved problematic, however, leading to dissension within the American dental profession. Eventually the controversy led to the dissolution of the American Society of Dental Surgeons in 1856.[133,134,143]

Then, as now, there were conflicting opinions as to the motives of the parties holding opposing views. Amalgam detractors maintained that monetary self-interest was the primary motive for amalgam supporters, who in turn downplayed the potential toxic effects of mercury.[143] Amalgam supporters, on the other hand, claim that those against amalgams were driven primarily by jealously, prejudice, and poor judgment.[134,245]

When the American Dental Association was formed to replace the defunct American Society of Dental Surgeons, it expressed no opinion on the safety of dental amalgam. In the meantime, there were ongoing efforts to develop a better amalgam and, in the late 1870s, a movement began within dentistry to promote amalgam as a valuable filling material even as reports of its potential deleterious effects were debunked.[134] By1895, the American Dental Association was expressing support for the use of amalgam, a position it has held consistently until the present.[198,246]

Detractors to amalgam were active throughout the 20th century,[143] and speculation about potential links between amalgam and various ailments were ongoing.[247,248] Concerns were also raised about potential occupational hazards for dentists and dental assistants who were exposed to mercury on an ongoing basis.[249-252] For the most part, however, the safety of amalgam was largely assumed until the 1980s when methods were developed that confirmed the steady release of mercury vapours from amalgam fillings.[253,254]

Although the American Dental Association acknowledged the persistent off-gassing of mercury vapour in the mouths of patients with amalgam fillings, it maintained that any mercury levels were clinically insignificant, while reasserting its confidence in amalgam.[206] In December of 1990, the American news program *60 Minutes* aired an exposé that proposed potential links to multiple sclerosis and other ailments due to poisoning from amalgam, placing the debate squarely in the public sphere once again.[255-257]

The 1990s was a decade of heightened activity in the amalgam debate. While some within dentistry maintained that no scientific studies showed amalgam to be unsafe,[258] complained that media hype was undermining a good product,[155,257] and even went so far as to equate amalgam concerns with witchcraft and astrology,[259] others doggedly questioned the

evidence in support of amalgam safety. Indeed, a persistent theme throughout the debate involves conflicting interpretations both of what constitutes evidence and what any supposed evidence means. Although numerous studies and supporting statements throughout the 1990s from North America and abroad affirmed the supposed safety of mercury amalgam, while debunking any connections to chronic diseases,[160,181,217,218,258,260-264] others questioned those conclusions: "The comparison of mercury exposure levels from dental amalgam with occupational exposure is illusive," states one commentator. "Occupational exposure is 40 hours per week (while amalgam exposure is 154 hours per week)... and continues uninterrupted during the entire lifetime of the restoration."[265] Another detractor argued that the interpretation of mercury toxicity is extremely difficult because of the variable half-life of mercury which can vary between tissues in the same individual.[132] Yet another refers to "good evidence" for delayed neurotoxicity from mercury exposure that may only be manifested many years later.[266] Others simply question the long-term safety of amalgam.[262] The potential connection between amalgam and chronic diseases such as multiple sclerosis[267] or mental illness[255,268] is also frequently raised.

Given the media attention and apparent lack of consensus, some patients insisted that their amalgams be removed. Dentists struggled to know how to respond.[269] Contrary to available evidence, one leading professional journal advised that, if asked, patients should be informed that when combined with other metals mercury becomes "a biologically inactive substance."[206] Some dentists simply refused to comply with patient requests, resulting in a 1993 case in Canada in which a dentist was charged with malpractice for refusing to replace a patient's amalgam fillings. While the Ontario Health Disciplines Board found that dentist innocent,[270] other dentists were more willing to grant their patients' requests, leading to charges of quackery and suggestions of exploitation.[180,181,271] The ongoing issue prompted the American Dental Association to revise its Principles of Ethics and Code of Professional Conduct to state: "The removal of amalgam restorations from the non-allergic patient for the alleged purpose of removing toxic substances from the body, when such treatment is performed solely at the recommendation or suggestion of the dentist, is improper and unethical."[171] The Canadian Dental Association followed suit with similar statements, maintaining that amalgam removal was unwarranted and unprofessional.[19,139,141,272] Meanwhile, dentists who questioned the use of amalgam continued to voice concerns and in some cases questioned the professional competency of those who maintained the status quo. Inasmuch as amalgam is relatively easy to work with compared to resin, some speculated that it was lack of skill that in part motivated many to resist the move to resin. "Amalgam is a material that is ideal for mediocre dentistry," opined one dentist.[273]

The Canadian contribution during this particular period was significant. While the official position of the Canadian Dental Association, in support of amalgam, has been documented, there were strong dissenting voices within the Canadian scientific community. University of Calgary researchers M.J. Vimy and F.L. Lorscheider were instrumental in developing techniques to measure concentrations of mercury vapour released by amalgams[254,274] and published a number of papers in medical and scientific journals throughout the 1980s and 1990s that raised concerns about mercury toxicity.[167,275] Their consistent conclusion was that research evidence does not support the notion of amalgam safety.[276] It should also be noted that professor Vimy was one of the scientists interviewed in the *60 Minutes* exposé of 1990.

As the public debate grew, the Medical Devices Bureau of Health Canada started its own investigation.[19] Dr. Mark Richardson was commissioned to attempt a calculation of the fraction of total exposure and relative risk due to mercury exposure from amalgam.

Richardson's report, released in 1995, was the first comprehensive risk assessment in Canada of mercury exposure from amalgam.[277] Richardson's study did not include laboratory research or clinical investigations but relied instead on sophisticated computer modelling techniques to arrive at a tolerable daily intake level for mercury. His initial simulations and calculations indicated that amalgam contributes about 50% of the daily mercury exposure for the average Canadian.[19,277]

Before releasing Richardson's study, Health Canada asked a group of international experts in toxicology, public health, and risk assessment to review it. While the reviewers generally agreed Richardson's methodology was sound, concerns were expressed over the lack of data on many of the crucial factors in his assessment model. Doubts were raised about whether probabilistic estimation techniques that relied on assumptions in lieu of data could provide a reliable tolerable daily intake.[19] Health Canada subsequently convened a committee of stakeholders to review the report. That committee initially included professor Vimy, but when it became apparent the Committee would not recommend accepting Richardson's calculation of the tolerable daily intake, Vimy resigned, complaining that the committee was stacked in favour of those supporting the use of amalgams.[278] Health Canada subsequently decided not to follow Richardson's recommendation,[19] and the Canadian Dental Association declared it "good news on amalgam." "Science, not misinformation and zealotry, must be the determining factors," declared the then-president of the Canadian Dental Association.[278]

Although Health Canada did not endorse Richardson's tolerable daily intake estimate, the stakeholder committee did approve eight recommendations including one related to potential amalgam toxicity. That recommendation is carefully phrased, however, and emphasizes that "there is no evidence that dental amalgams contribute to immunological, neurological, or kidney disease." However, given that there is some evidence that mercury exposure from all sources could have potential negative effects, dentists and physicians were advised to consider these concerns in their choice of dental materials,[19] although even these somewhat innocuous recommendations were challenged by Canadian dentists.[279] This Canadian response contrasted with what was occurring in many European countries.

Even as WHO and the FDI were issuing a 1995 consensus statement reaffirming the safety of amalgam, while emphasizing its cost-effectiveness,[164] the conversation had taken a somewhat different turn and tone in Europe. Already in 1987, the Federal Office of Public Health in Germany issued a series of recommendations against the use of amalgam for pregnant women, children, and people suffering from kidney disease. By 1992, the Swedish parliament was considering a total ban on amalgam, and had already disallowed its use for patients less than 20 years of age.[19] The total Swedish ban did not occur, however, until 2009 and, when announced, was primarily out of environmental as opposed to patient safety concerns.[280] This shift in focus to emphasize public health and environmental concerns was to become a common theme as the amalgam issue moved into the new millennium.[187,281] Nevertheless, in the 1990s, patient safety was still the motivating factor throughout Europe. In 1998, the Department of Health in Britain advised dentists against using amalgam during pregnancy, following the leads of Sweden and Norway, where such restrictions had been in place since the late 1980s. While Finland and Denmark did not specifically highlight pregnancy, they had issued general recommendations against amalgam use. Germany and Austria followed suit, issuing recommendations to reduce amalgam use in young children, pregnant women, and in individuals with kidney disease [282] — this last ostensibly based on evidence that mercury accumulates in solid organs of the body and especially the kidneys and liver. [275]

As the amalgam controversy moved into the 21st century, the lines of disagreement regarding patient safety have remained essentially the same. While various studies maintaining either that mercury toxicity from amalgam is not clinically significant,[283] or studies purportedly demonstrating that those exposed to mercury vapours did not exhibit any particular deleterious effects from such exposure,[47,48] others continue to dispute both the findings and the methods used in reaching those conclusions.[144,284] "Although the issue of amalgam safety is still under debate," says one recent review, "the preponderance of evidence suggests that mercury exposure from dental amalgams may cause or contribute to many chronic conditions."[212] Yet the temptation to cast aspersions on the opposing position is ever-present: "Google amalgam," complains one amalgam supporter, "and you'll be overwhelmed by junk science and fraud."[221] Nevertheless, the calls for additional research on the long-term effects of mercury exposure remain constant.[285-288] Despite the Canadian Dental Association's continuing support for the use of amalgam, a 2002 survey of Canadian dentists identified the development of materials other than amalgam to be a research priority.[289]

Other areas of potential research have emerged in recent years including the role of genetics in identifying patients who may be more susceptible to mercury toxicity,[210,211] as well as the potential impact of electromagnetic fields including magnetic resonance imaging (MRI) scanners in elevating mercury toxicity levels for those with amalgam fillings.[97,162,290,291]

While the ongoing questions regarding patient safety have remained consistent, there are three areas of heightened activity in the 21st century worth noting. The first concerns the increased level of litigation. Due in part, no doubt, to the heightened public awareness of amalgam throughout the 1990s, a number of lawsuits were launched in a various jurisdictions (primarily in the US) against dental associations, either claiming harms from the continued use of amalgams or seeking legislative restrictions on such use.[146,147,151,152] Virtually all such cases were dismissed. However, not all cases were decided in favour of those supporting the use of amalgams. Cases in both Oregon and California challenged the relevant dental associations' attempts to restrict the kinds of information dentists could share with their patients about potential amalgam toxicity, which the plaintiffs perceived as "gag orders." In both cases, the courts ruled in favour of the plaintiffs.[148,149] Such legal proceedings were instrumental in the FDA's 2009 decision to reclassify dental amalgam.[150,292] In particular, the FDA documentation reports that 70% to 80% of inhaled mercury vapour is absorbed by the lungs and distributes to several organ systems in the body, including a fraction that crosses the blood-brain barrier. Although the FDA reclassification document concludes there is inadequate evidence to conclude that vulnerable populations are at risk, it includes "special controls" for developing fetuses, breastfed infants, and children under six.[292]

The second development, which bears noting, is the rise in the use of composite resins as an alternative to amalgam. Whether out of concern for safety or simply as a matter of aesthetic preference, composite resins have been gaining in popularity throughout the past two decades. While concerns have also been raised about the potential toxic effects of BPA as a by-product of composites,[170,293,294] the evidentiary basis for these concerns is also disputed.[295]

Finally, a rise in concerns about environmental protection in general, and about mercury toxicity from all sources in particular, has had a significant impact on the amalgam discussion in the 21st century. Canada has recently ratified the Minamata Convention — an

international effort to reduce human-generated mercury emissions.[131] Such international efforts have raised questions about the future role for amalgam in dentistry,[296] and about the potential impact on dental patients.[297,298] While international bodies still maintain the safety of amalgam as a dental material, it nevertheless supports a phase-down in use [165,166]

The debate over the safety of dental amalgam as a restorative material has been long and sustained. If there is any semblance of common or neutral ground, it is around the growing consensus that dental amalgam contributes to the overall environmental load of mercury toxicity, and efforts to limit and reduce its impacts are appropriate.

Finally, it is worth mentioning the precautionary principle which is often invoked "in circumstances where there is some evidence that a particular activity may result in health or ecosystem damage, but great uncertainty as to the potential magnitude or nature of those impacts." [182] Tickner and Coffin summarize the relevance of this principle to the mercury amalgam issue, as follows:

> A precautionary approach to mercury amalgams would consider the clear evidence of mercury toxicity, the lifecycle risks of amalgams, and a broad range of alternatives. While the potential health risks from mercury amalgams to healthy adults with fillings is likely low, one must consider the lifecycle of the amalgam, including cumulative exposures and the potential for greater impacts when exposures occur at sensitive times in development — pregnancy, childhood. This case illustrates the challenges of alternative assessment — in finding those that are both effective and safe — and the trade-offs that are often involved. However, the lack of currently available alternatives should not stall intermediate action to minimize exposures to mercury. (p12)[182]