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CADTH HEALTH TECHNOLOGY ASSESSMENT

Composite Resin versus Amalgam for Dental Restorations: A Health Technology Assessment — Project Protocol

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Background & Rationale

Dental caries is a significant oral health problem worldwide.[1] While the epidemiology of dental caries across time and populations has changed — due to 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 activities of daily living.[2] In Canada, data from 2007 show that 57% of children aged 6 to 11 years, 59% of adolescents aged 12 to 19 years, and 96% of adults have a history of dental caries.[3]

Standard treatment for dental caries aims to restore the structure of the affected tooth using filling material to replace decayed dental tissue.[4] Amalgam fillings have been widely used for more than 150 years[5] and evidence suggests that amalgam has been an effective and affordable dental restorative material.[5-7] Some factors supporting the widespread and enduring use of amalgam as a dental restorative material include its strength, durability, and low cost.[8]

However, because amalgam is partly composed of elemental mercury, concerns have persisted over its safety for human health.[9] 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.[8-10] Similarly, the placement and removal of amalgam fillings exposes patients and dental personnel to low levels of mercury vapour.[10] Mercury is absorbed by and accumulates in bodily organs and tissues, and is known to easily cross the blood-brain and placental barriers. Depending on the level of exposure, mercury can cause significant adverse health effects, including neurological and kidney diseases.[9] While these potential harms have raised concern, current evidence suggests that the very low levels of mercury exposure from dental amalgam fillings do not pose a serious risk to human health.[5,8]

In addition to the potential health effects from mercury contained in dental amalgam, there are concerns regarding the environmental impact of mercury released from amalgam waste generated by dental offices.[9,11] The placement or removal of amalgam fillings produces amalgam debris, which can be introduced into the environment through wastewater from dental offices.[11] Mercury is designated as a toxic substance under the Canadian Environmental Protection Act, 1999.[12] Waste management initiatives and requirements introduced in recent years for Canadian dental facilities have contributed to a significant reduction of discharges of amalgam waste to the environment.[13] Nonetheless, the perceived health risks and potential environmental impact of dental amalgam, and the mercury it contains, continue to feed a certain amount of debate over its use in dentistry.

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.”[14] In addition to the use of mercury in general, the Minimata Convention specifically addresses the use of amalgam in dentistry.[14] One concern arising from the proposed phasing out 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.[3,8] Canada signed the Minamata Convention in 2013[15] and ratified it in April 2017.[16] As of May 31, 2017,[17] the Convention had been ratified by 54 governments and will enter into force internationally on August 16, 2017.[18]

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.[19] 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.[5,20] 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.[6,21] Nonetheless, evidence has shown that long-term failure rates of fillings made of composite resin are greater than those made of amalgam.[5] In addition, the placement of restorations made of composite resin involves a more demanding, time-consuming procedure than that for restorations made of amalgam.[6,21] 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.[21] Evidence also suggests that restorations made of composite resin have both a higher initial and long-term cost compared with those made of amalgam.[22]

Concerns have also been raised about the safety of composite resin restorations due to 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)."[23] (p. 447) It is suspected that these substances may have deleterious effects on human reproductive and metabolic systems, and limits have been recently lowered on levels of exposure thought to be safe.

Given the concerns that affect populations, patients, dental practitioners, and payers, as well as the significant clinical, cost-related, environmental, and other ethical considerations, a comprehensive evaluation of the benefits, harms, and other consequences of dental restorations made of composite resin versus amalgam is essential.

Policy Question

Should dental amalgam continue to be used in Canada?

Objectives

To optimize the clinical and Canadian contextual relevance, as well as the scientific rigour of this Health Technology Assessment (HTA), its aim is to inform the policy question through a comparative assessment of dental amalgam and the most commonly used alternative (composite resin). Specifically, the HTA will address the comparative efficacy 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. An analytic framework for the HTA can be found in Appendix 1.

Research Questions

The HTA will address 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?

Ethics:

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

Implementation Issues:

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

Environmental Assessment:

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

Methods

To inform the preparation of this protocol, a preliminary scoping review of existing HTAs and systematic reviews (SRs) was conducted. The protocol was developed a priori, and will be followed throughout the HTA process. This protocol has also been prospectively registered in the PROSPERO database,[24] and any deviations will be disclosed in the final report. Likewise, any updates will accordingly be made to the PROSPERO submission.

Research question 1 will be addressed by updating a 2014 Cochrane SR that investigated the efficacy of direct, composite resin fillings versus amalgam fillings in permanent, posterior teeth. The update will aim to adhere to the scope and methods as described in the

published review's report.[5] Question 2 will be addressed through a de novo SR of published clinical evidence. Question 3 will be addressed through an Environmental Scan and cost-consequence analysis. Question 4 will investigate patient experiences and perspectives through an SR of qualitative evidence. Ethical issues (question 5) will be investigated using a literature review, and implementation issues (questions 6 to 8) using a multi-stage, sequential research protocol, including in-person, telephone, or email consultations; a review of the published literature; and, if deemed necessary, a survey of relevant decision-makers in dental care in Canada. The environmental assessment (question 9) will be carried out using a literature review.

Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy.

For the clinical search, published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–) with 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 (to June 19, 2017) will be searched by an information specialist at the Cochrane Oral Health group. The LILACs via BIREME Virtual Health Library will also be searched for question 1, in accordance with the methods carried out in the 2014 Cochrane SR.[5]

The search strategy will use both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. For question 1, the search conducted for the 2014 Cochrane SR[5] search will be updated. The main search concepts will be dental amalgams and composite resins. For this search, no methodological search filters will be applied. The retrieval will be limited to documents published since January 2012. No language limits will be applied. Conference abstracts will be included in the search results. For question 2, the main search concepts will be dental amalgams and composite resins. For this search, an adverse events filter will be applied. Conference abstracts will be excluded from the search results. For the dental amalgams safety search, retrieval will not be limited by publication year. For the composite resins safety search, the retrieval will be limited to documents published since 2006. See Appendix 2 for the detailed search strategies.

Five additional searches will also be performed: economic studies, patient experience, ethics, implementation, and environmental assessment. The same main concepts — dental amalgam and composite resins — will be used for these additional searches.

Economic studies will be identified by searching the following databases: MEDLINE (1946–) via Ovid; Embase (1974–) via Ovid; and the NHS Economic Evaluation Database via Ovid. Conference abstracts will be included in the searches. The searches will not be limited by language or publication year.

Patient experience information will be identified by searching the following databases: MEDLINE (1946–) via Ovid and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO. The searches will not be limited by language or by publication year.

Ethics-related information will be identified by searching the MEDLINE (1946–) via Ovid and CINAHL via EBSCO. The searches will be limited to English- or French-language publications but will not be limited by publication year.

Implementation-related information will be identified by searching MEDLINE (1946–) via Ovid and CINAHL via EBSCO. The searches will be limited to English- or French-language publications but will not be limited by publication year.

Environmental assessment–related information will be identified by searching the following bibliographic databases: MEDLINE (1946–) via Ovid and Embase (1974–) via Ovid. Conference abstracts will be excluded from the searches. The searches will be limited to English- or French-language publications but will not be limited by publication year.

The initial search will be completed in June 2017. Regular alerts will be established to update the search until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. 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. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for the report.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of health technology assessment agencies, clinical guideline repositories, SR repositories, economics-related resources, and professional associations. Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. See Appendix 2 for more information on the grey literature search strategy.

Clinical Review

The protocol for the clinical review has been developed in consideration of the PRISMA-P checklist[25] for guidance on clarity and completeness.

Study Design

To address the first question, an update to a 2014 Cochrane SR[5] will be carried out, due to the consistency of its scope and methods with those planned in the current protocol. The second question, addressing safety outcomes, will be addressed via a de novo SR of the evidence describing the safety of dental restorations made of composite resin versus amalgam.

Study Eligibility

Eligibility criteria for clinical studies are outlined in Table 1.

Table 1: Clinical Review Study Selection Criteria

	Question 1	Question 2

Population	• Permanent, posterior teeth affected by dental caries	• 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 based on the following:
		  ○ patient age (if not otherwise defined within the study):
		  ▪ children (0 to 5 years; 6-11 years; 12-17 years)
		  ▪ adults (18 to 64 years)
		  ▪ older adults (65 years and older)
		  ○ genetic susceptibility
		  ○ socioeconomic status
		  ○ remote, rural, and urban settings
		  ○ people with developmental/ 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 un-bonded
	  ○ 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 outcomes restricted to the following:
	• primary:
	  ○ restoration failure rate
	• secondary (i.e., reasons for failure):
	  ○ secondary caries
	• tooth fracture
		All adverse events, including:
		• sensitivity
		• toxicity
		• allergic reaction
		• injury

Time Frame	• January 2012–present (in accordance with an update to Rasines-Alcaraz et al.[5])	• January 2007–present
Study Design	• RCTs ○ minimum 3-year follow-up	• RCTs; primary, non-randomized studies that directly compare composite resin and amalgam restorative materials

RCT = randomized controlled trial.

Full-text publications that meet the criteria outlined in Table 1 will be included. Duplicate publications will be excluded, as will multiple publications of the same study, unless they provide unique methodological details and/or findings of interest. Eligible studies will be full, published, or unpublished reports (i.e., no conference or meeting abstracts or other summaries that lack detail concerning study methods and findings).

Specific to question 1, exclusionary criteria will replicate those established in the original SR that we aim to update. Specifically, studies will be excluded if they focus on restorations in anterior teeth (where amalgam is rarely used[5]), deciduous teeth, and/or endodontic restorations. Restoration failure will consider both durability (survival) and insertion success rate. Further, because short-term follow-ups in the study of dental restorations are less informative,[26] studies with less than three years of follow-up will be excluded. Study designs of interest will be limited to randomized controlled trials (RCTs) only, in accordance with the methods employed in the original SR that we aim to update.[5] Any deviations from the methods used in the original SR will be elaborated in the final report.

For question 2, no limits on the age of patients, types of composite resin, or amalgam dental restorations will be imposed. Where possible, and in anticipation of studies that may describe participants with both restorations made of composite resin and those made of amalgam, exposure will be defined by surface area (either number of surface areas per type of material per person), or surface years (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. Likewise, where reported, exposure will be considered “ever exposed” versus “never exposed,” e.g., in cases where amalgam restorations have been removed but were once present. All adverse events will be considered, including toxicity (e.g., mercury levels, bisphenol A levels, and associated neurologic function), renal function, immune function, reproductive function, fetal and neonatal effects, neurobehavioral 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). While no restrictions will be imposed on the follow-up duration for the review of safety and/or harms, study designs that do not directly compare composite resin and amalgam restorations will be excluded. Instead, only primary studies that directly compare amalgam versus composite resin (i.e., RCTs and non-randomized studies with a comparative design that involves a prospective or retrospective cohort, case control, nested case control, and/or case-cohort) will be included. Reviews, meta-analyses, and HTAs will be excluded, as will in vitro and modelling studies.

Study Selection

Study selection will be conducted using DistillerSR,[27] and standardized screening forms (Appendix 3) will be operationalized. Two reviewers will independently screen titles and abstracts of all citations retrieved, and those deemed potentially relevant by either reviewer will be retrieved in full. The same reviewers will then independently apply the criteria outlined in Table 1 to the full-text reports and compare their selections, resolving discrepancies through discussion until consensus is reached, and involving a third reviewer as necessary. Regular reviewer meetings will be held during both phases of screening to review selection discrepancies and establish consensus on the application of selection criteria.

Kappa statistics will be calculated to measure agreement between reviewers at both phases of study selection. Calculated values will be interpreted as follows: < 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 > 0.80 as almost perfect agreement.[28]

The final, draft list of included studies will be posted for stakeholder review for 15 business days, during which feedback and any additional studies identified for potential inclusion will be reviewed. Final lists of included and excluded studies (with a rationale for each of the latter) will be presented in the final report.

Data Abstraction

Data abstraction for included studies will be conducted in DistillerSR.[27] A standardized data abstraction form (Appendix 4) has been designed to abstract relevant information from included studies, including:

- First author's name, publication year, country, and funding sources
- Study design
- Description of outcomes reported, follow-up duration, and study loss to follow-up
- Description of subgroup and/or meta-regression analyses of interest
- Results and conclusions regarding the outcomes and subgroups 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, numbers of surface areas and/or surface years
    - adverse events, including any of relevance to sensitivity, toxicity, allergic reaction, and injury
    - from non-randomized studies, unadjusted (crude) and adjusted results, along with a list of factors included in the adjusted models.

Two reviewers will pilot the data abstraction form, in duplicate, on a representative sample of included studies until consistency is reached. Following calibration, data from each included study will be extracted by one reviewer and verified by a second reviewer. Disagreements will be resolved through consensus, consulting a third researcher as necessary. Data will not be abstracted from figures if they do not explicitly provide relevant, numerical data. Where a lack of clarity is identified in any included report of findings, authors will not be contacted to provide missing information.

Risk of Bias Assessment of Included Studies

For question 1, the Cochrane Risk of Bias Tool[29] will be used to assess included RCTs, in accordance with the methods implemented in the 2014 SR.[5] For question 2, it is acknowledged that there are unique considerations when assessing the risk of bias in studies of harms and/or adverse events.[30] Nonetheless, to date, there is a dearth of guidance available to inform a systematic approach. Thus, we will assess the overall risk of bias for included studies using standard tools, specifically the Cochrane Risk of Bias Tool[29] for RCTs and the ROBINS-I[31] tool for non-randomized studies. The Cochrane Risk of Bias Tool[29] solicits information on seven items across six domains. For each item, a judgment of "Low Risk of Bias," "High Risk of Bias," or "Unclear Risk of Bias" will be assigned and used to indicate an overall judgment of "Low Risk of Bias," "High Risk of Bias," or "Unclear Risk of Bias" to each study, in accordance with guidance published in the Cochrane Handbook.[29] ROBINS-I[31] allows for the assessment of risk of bias across 34 potential items in seven domains. Each item is answered "yes," "probably yes," "probably no," "no," and "no information," with "yes" indicating low concern of a risk of bias, and "no" indicating significant concern. Risk of bias per domain per study will be assessed as "low," "moderate," "serious," "critical," or "no information," and used to assign an overall judgment of "low," "moderate," "serious," "critical," or "no information" to each study in accordance with ROBINS-I guidance. As it concerns the particular methods used to define, ascertain, and report harms and adverse events, additional sources of potential bias will be considered and reported if and where identified.

Two researchers will pilot and independently assess the risk of bias of the included studies. Disagreements between reviewers regarding assessment of risk of bias will be resolved through discussion and consensus, consulting a third researcher when necessary. The findings of the risk of bias assessments will be reported for each included study for both questions 1 and 2. Although the results of these assessments will not be used to further include or exclude studies, the conclusions and discussions will focus on the findings of the studies deemed to be at a lower risk of bias.

Assessments of meta-bias — the quality of the body of evidence identified and assessed concerning the comparison of dental composite resin and amalgam as restorative materials for dental caries — are not planned.

Data Analysis

Statistical Synthesis

The decision to pool quantitative outcome data will be considered separately for questions 1 and 2, and will be informed by several factors, including the number of included studies, and the amount of between-study clinical and methodological heterogeneity.

Where deemed appropriate, statistical syntheses will be conducted using Review Manager software (RevMan), version 5.3.5[32] (or the most up-to-date version of the software available at the time of analysis) and forest plots will be presented for summary estimates. Meta-analyses will be conducted using random-effects models, unless otherwise indicated.

Dichotomous outcomes will be pooled using risk ratios (RRs) and 95% confidence intervals (CIs) will be calculated. For question 2, depending on the effect measures presented in the individual studies, either pooled RRs or odds ratios (ORs) will be calculated. Conversion to a common effect measure may be necessary to facilitate meta-analysis, and will be guided

by the data. For time-to-event data such as restoration failure, pooled hazard ratios and 95% CIs will be calculated. Continuous data will be meta-analyzed using a mean difference or a standardized mean difference with corresponding 95% CIs.

For question 2, RCTs and non-randomized studies that report data on the same outcomes will be pooled separately.

Heterogeneity

Statistical heterogeneity will be assessed using the I^2 statistic, which quantifies the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). I^2 values less than 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% represents considerable heterogeneity.[33] The heterogeneity will be considered statistically significant if the *P* value (for Cochran's chi-squared test) is < 0.1.

Subgroup Analyses

Depending on the amount of available data and the degree of observed statistical heterogeneity, the following sources of heterogeneity may be explored, depending on the availability of data, using subgroup analyses:

- participant age
- genetic susceptibility to mercury
- socioeconomic status
- remote, rural, and/or urban setting
- developmental/special need
- numbers of restorations/surface areas/surface years
- application technique used to place the restoration

Sensitivity Analyses

Sensitivity analyses may be considered (particularly for question 2) to evaluate the robustness of findings by methodological and statistical factors, including (but not limited to) the impact of varying study quality assessments, alternative study designs (e.g., cohort versus case control), types of analysis (e.g., unadjusted versus adjusted), and effect measures (e.g., RR versus OR).

Narrative Synthesis

Whether or not statistical syntheses are appropriate (as above) and conducted, a narrative synthesis will be presented, including the presentation of findings within summary tables, alongside study and clinical characteristics believed to contribute to heterogeneity. A narrative description will aim to synthesize the direction and size of any observed effects across studies, and will include an assessment of the likelihood of clinical benefit and/or harm.

Report of Findings

The final report describing the clinical efficacy and safety of dental composite resin compared with amalgam will be prepared in consideration of relevant reporting guidelines for SRs, i.e., PRISMA,[34] PRISMA harms,[35] and MOOSE.[36]

Economic Review

To address research question 3, a cost-consequence analysis will compare costs and health outcomes associated with dental amalgams and composite resin as dental restorative materials for permanent posterior teeth. A cost-consequence analysis is a disaggregated approach in which costs, benefits, and harms are not combined but reported separately.

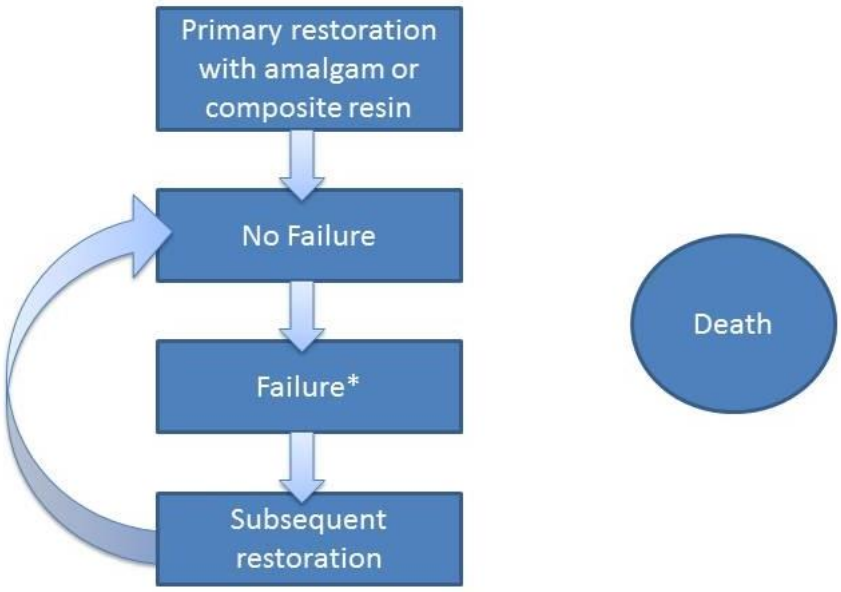
A Markov model will be constructed in Microsoft Excel to calculate the outcomes associated with the two types of dental restorative materials. Given the variability in who reimburses or pays for dental services in Canada, the primary perspective will be societal. To capture the consequences of more frequent restorations (e.g., need for larger restorations or more complicated procedures), a lifetime horizon will be the preferred approach. However, if the necessary data (e.g., risks or rates of subsequent restoration failure) are not available, a shorter time horizon may be defined. The findings will be presented discounted at 1.5%,[37] with costs reported separately according to who incurs the costs.

The economic analysis will be aligned with the clinical review in terms of classes of restoration of permanent teeth and reasons for restoration failure, with the unit of analysis based on the individual restored tooth. Figure 1 presents a preliminary structure of the Markov model that will be developed to calculate the health outcomes and costs associated with each dental restoration strategy. Note that the failure state has been simplified in this figure. The model will focus on the two most common reasons for restoration failure leading to restoration replacement (secondary caries and tooth fracture). A third failure type, “other reasons,” will capture all other reasons for restoration replacement and will be computed as follows:

1 – [probability of secondary caries] – [probability of tooth fracture]

Management of restoration failures include the possibility of having larger restorations, including crowns with or without root canal treatments.

Figure 1: Structure of Markov model comparing different strategies to restore tooth caries



*This state has been simplified for the figure. The failure state will be further subdivided into the 3 types of failure (i.e., secondary caries, tooth fracture, others) with the possibility to have larger restorations (including crowns with or without root canal treatment) as subsequent failures occur over the lifetime of the tooth.

To ensure the model reflects Canadian clinical experience, feedback will be sought from dental experts and the model structure may be revised based on their comments.

Non-Monetarized Outcomes

Outcomes of interest to this model will be partly dependent on the results of the clinical and environmental review. This may include the average lifespan of the dental restorative material, the rates of adverse events, and the level of exposure to toxic materials (e.g., mercury for dental amalgams, bisphenol A for resin composites).

Resource Use and Costs Outcomes

The costs captured in the model will reflect the scope of the clinical review and the perspective of the economic analysis. Costs categories of interest include the procedure cost and cost of waste management programs (e.g., amalgam separator and recycling).

Canadian-specific costs will be used, when available. In particular, fee schedules (e.g., publicly funded dental program fee schedules, provincial dental association suggested fees, publicly available insurance fee schedules) for dental restorative procedures in Canada will be used. The costs of the procedures will be informed by a CADTH Environmental Scan on the cost of dental restorative procedures in Canada. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs

will be adjusted to 2017 Canadian dollars, using the health care component of the consumer price index.

Sensitivity Analysis

To reflect the uncertainty that exists around the model inputs, and hence the results of the economic model, a probabilistic analysis will be performed. As noted, the cost-consequence analysis will list separately all direct and indirect costs, and will separately catalogue the different outcomes associated with each strategy. To address heterogeneity in both costs and clinical outcomes, a scenario analysis will be performed. Subgroups of potential interest may include:

- Population age: children, adults, the elderly
- Setting: remote, rural, and urban.

Assumptions

During the course of the model development, assumptions and limitations will be identified and acknowledged in the report. Assumptions will be tested through the conduct of sensitivity analyses, where possible.

Patient Perspectives and Experience

Study design

A systematic review of qualitative evidence.s

Types of participants

This review will consider studies that include the perspectives and experience of patients (adults or children) around dental amalgam and composite resin restorations.

Phenomena of interest

The phenomena of interest for this review include:

- The patients' perspectives on and experience with the use of mercury/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/amalgam for dental restoration for either themselves or their children.

Context

The context for this review is the patients' 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). Mixed-method studies will be included if these studies have a qualitative component and participant voice data that addresses this review question.

Screening and study selection

Citations will be screened by two independent reviewers using the Covidence data management software. The process of screening entails two phases. First, the full set of citations will be screened based on title and abstract (if available). Following that, citations will be screened based on full-text reading. Any discrepancies will be resolved by consultation with a third reviewer.

The final set of studies will be exported from Covidence and imported into SUMARI — the Joanna Briggs Institute (JBI) software designed to manage the process of evidence synthesis. 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 will be conducting a meta-synthesis of the qualitative evidence.

Types of studies

The review will consider studies that focus on qualitative data including, but not limited to, designs such as phenomenology, grounded theory, ethnography, action research, and feminist research.

Assessment of methodological quality

Qualitative papers selected for retrieval will be assessed by two independent reviewers for methodological quality using standardized critical appraisal instruments from the JBI Qualitative Assessment and Review Instrument (JBI-QARI).[1,2] Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data extraction

Qualitative data will be extracted from papers included in the review by two independent reviewers using the standardized data extraction tool from JBI-QARI.[38] The extracted data will be stored in the QARI software and will include specific details about the interventions, populations, study methods, and outcomes of significance to the review question and specific objectives. These descriptive data will be presented in a table of characteristics of included studies.

Data synthesis

Primary research of qualitative evidence typically generates one or more themes that reflect the participants' voices on the topic. Themes that answer this systematic review question will be extracted. These qualitative research findings themes, called findings in the JBI methodology of synthesis, will be pooled using JBI-QARI.[38] The process of pooling involves the aggregation or synthesis of these 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.[39] 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 will then be subjected to a meta-synthesis to produce a single comprehensive set of synthesized findings that could be used as a basis for evidence-based practice. Where there is considerable discrepancy in the findings, indicated by a complete lack of similarity of meaning that would preclude the

aggregation of the findings into categories, the findings will be presented in narrative form. This approach describes the findings as individual concepts rather than as aggregated categories.

Ethical Issues

The purpose of this analysis is to identify and reflect on key ethical concerns that should be considered when comparing the use of dental amalgams and resin composites for the repair of dental caries in Canada, and/or for the replacement of dental fillings. Though other sections of this HTA implicitly touch on ethical concerns broadly, the aim of this analysis is to make such issues explicit and to identify others that may be relevant to any decisions in this regard.

The issues raised in this section go beyond narrowly defined ethical concerns to encompass broader, social and legal implications as well (so-called ESLIs). It is common in the ethics literature, across a broad range of health-related issues, to refer to ELSIs when addressing broader values-related considerations. As mercury is an essential component of dental amalgams that poses environmental risks related to the use and disposal of amalgam materials, it is anticipated that environmental concerns will be a significant factor in the ethical analysis.

Further, institutional arrangements (e.g., privately funded versus publicly funded dental care) may also affect our views and expectations of dental care delivery. For example, privately funded dental care users may be viewed primarily as consumers who are purchasing a product. In this case, the onus is primarily on the consumer to make informed decisions about the product to be purchased (caveat emptor). The role of government in this regard is characterized mainly in terms of consumer and environmental protection. Conversely, publicly funded dental care may be viewed as a public health service in which users are viewed primarily as patients. This may entail a greater regulatory burden for the government to protect the users of such services, and a concomitant fiduciary responsibility of the dental professionals to provide safe and effective treatments.

Ethical considerations related to the over-arching research question will be addressed through the following questions:

1. a) What is the appropriate balance between government oversight/intervention versus individual control and/or responsibility (for both providers and recipients) with regard to the choice between amalgams or composites?

   b) How do we balance competing values in this regard (e.g., financial costs, aesthetic preference, health and safety, environmental protection)?

2. Does the manner in which dental care is funded (i.e., through private or public insurance) affect the manner in which various ethical concerns are addressed?

Inquiry

The nature of bioethical analysis requires a two-step approach to identifying potential issues.

The first is a review of the ethics, clinical, and public health literatures to identify existing ethics analyses of the technology. The second is a novel ethics analysis based on gaps identified in the literature and the results of concurrent reviews. This may require selective

searches to provide the basis in theoretical ethics, in applied ethics analyses of similar technologies, and in evidence for the ethics analysis of emerging issues specific to dental amalgams and resins. Through this approach, we identify and assess the relative importance and strength of the identified concerns and proposed solutions, identify and assess issues that have not yet come to the attention of ethics researchers, and describe the values or principles that possible solutions must live up to where such solutions have not yet been proposed.

As this process involves ethical concerns, the analysis will reflect on the specific details of community and patient perspectives, clinical utility, economic analysis, environmental impacts, and implementation considerations. As such, the ethics analysis involves an iterative process that is responsive to results emerging from clinical, implementation, patient perspective, and economic reviews.

Review of the Bioethics Literature

A review of the empirical and normative bioethics literature will be conducted to identify material relevant to the identification and analysis of the potential ethical issues related to the use of amalgams and resins. We will search for reports that explicitly and specifically raise ethical issues related to the central question of this HTA, as well as literature not explicitly about ethical issues but, when read through an ethics lens, may raise or point to potential ethical issues, even if the participants and researchers did not formulate them as such. Such literature would include, for example, an empirical investigation of patient attitudes about amalgam versus composite resin in dental care.

Literature Screening and Selection

The selection of relevant literature will proceed in two stages. In the first stage, the title and abstracts of citations will be screened for relevance by a single reviewer. Articles will be 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 does not figure in the article-selection criteria; any identification of an issue by the public, patients, health care providers, researchers, or policy-makers is of interest whether or not it is 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 will be reviewed by the same reviewer. Reports meeting the above criteria will be included in the analysis, and reports that do not meet these criteria will be excluded from analysis.

Data Extraction and/or Abstraction Strategy

The bibliographic details for each report (e.g., author, publication date, journal), the potential ethical issues raised, and the report's conclusions (issues identified, values at stake identified through normative analysis, solutions proposed, and their normative justification, if presented) will be summarized in a table.

Analysis

The ethical issues identified, values described, and solutions proposed in the literature will be evaluated using the methods of ethical (applied philosophical) analysis, which includes: applying standards of logical consistency and rigour in argumentation, particularly where specific implications are identified and specific solutions advocated; responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; adequacy to the context for which the technology is being considered; and the representation of perspectives from diverse relevant communities, particularly attending to the possibility of the neglect of marginalized and vulnerable populations.

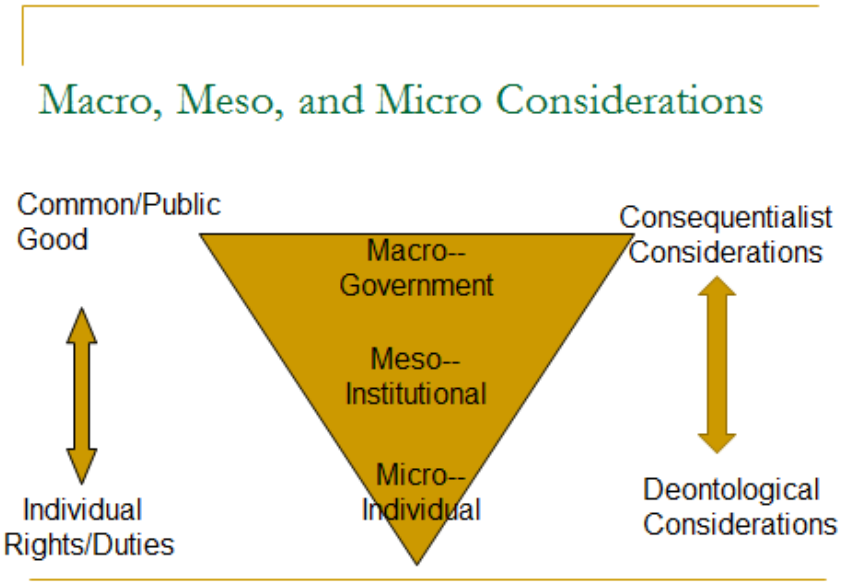
The proposed analysis will draw most directly on two classic perspectives that are well established in the health ethics literature, namely the utilitarian/consequentialist approach, and the deontological/duty-based approach. The former focuses on the overall consequences of a particular course of action 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. In other words, from a deontological perspective the most important consequence to consider is whether individual rights are properly honoured and accounted for irrespective of whether some supposedly greater good might be accomplished by ignoring 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. Depending on the nature of the issue and the context in which it arises, it is possible that other normative ethical perspectives may be invoked in the analysis (e.g., virtue theory may be particularly relevant to issues regarding professional conduct of dental professionals).

For the purposes of analysis, 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 a ministry of health and associated departments such as an office of public health. This approach is particularly appropriate in the present context as the use of amalgams versus composites may raise concerns of public health (a largely consequentialist, macro-level concern). Meso-level issues generally arise at the institutional level and include regulatory concerns at various levels of government and professional bodies. Micro-level concerns are those that affect individuals, whether they are patients, consumers, or providers of services (deontological issues).

As the foregoing indicates, an ethics analysis of amalgams versus composites in dental care raises a variety of issues ranging from broad public health and environmental concerns to more specific issues involving patient and consumer rights, the duties of individual providers and professional bodies, as well as regulatory issues that may vary depending how the product or service provided is characterized.

Figure 2 illustrates the analytical 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 2: Levels of decision-making and types of ethical consideration



Summarizing and Presenting Results

The reporting of ethical issues will follow the key values identified or issues being explored and will be determined by the values and issues that are identified. For example, the results may be summarized according to a principlism framework (issues concerned with autonomy, beneficence, non-maleficence, and justice) or by categorizing moral concerns as micro-, meso-, and macro-level issues. Regardless of the framework selected, the implications of the choice of framework on how the findings are presented and interpreted will be described. In addition, where the report undertakes analysis that is not derived from the peer-reviewed literature will be noted in the interests of transparency.

Ethical analysis assists in social and policy decision-making but is not itself the site of legitimate social decision-making, which requires consultation with and deliberation by relevant stakeholders in a given context. Decisions will also be sensitive to emerging empirical evidence. Furthermore, the ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and

consistency of service within a population, for example, are determined by facts about how health care services are arranged and provided.

Given these features of ethical decision-making, results of the ethics review will be presented in a way that helps decision-makers better understand the ethical implications of the decisions and recommendations they come to. For example, a number of contextualizing questions will be based on the identified issues so decision-makers can assess localized impacts, and proposed solutions will be analyzed to indicate the relevant ethical trade-offs at stake and mitigation strategies that could be employed to manage these trade-offs.

Implementation Issues

Research questions 6 through 8 aim to gather information around relevant implementation considerations for using dental amalgams and composite resin fillings in Canada. Implementation considerations may include policies, funding, and dental care practices relevant to 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 settings, a multi-stage, sequential research protocol will be followed. Findings at each stage will inform the need and scope of the next stage of research. The stages may include telephone or email consultations, a review of the published literature, and a survey. A detailed description of the methods followed to retrieve relevant data will be included in the final report.

Data Collection

Stage 1: Interviews

Interviews will be conducted with targeted experts and stakeholders identified through the clinician networks managed by CADTH's knowledge mobilization team 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 as well as specific literature that may be important to incorporate. These stakeholders may include dental care clinicians, dental program administrators, or other appropriate users, experts or decision-makers. One or two stakeholders from each relevant group will be approached, but this number could change depending on the information provided (e.g., depth of information, further referrals to other relevant stakeholders).

To guide the interviews, a semi-structured interview guide will be developed. Interview questions related to implementation will be developed based on research questions and the type of expert being consulted. Interviews will be conducted by telephone by a knowledge mobilization officer and follow-up questions or clarifications will be conducted by email. Notes will be taken during the interviews and copies of email correspondence will be retained for the purpose of subsequent analysis. Consent to publish comments and names will be sought, if required.

Stage 2: Literature Search

The literature search strategy for the implementation review is described in the corresponding Methods section of the protocol. A targeted literature search for Canadian published studies will be performed by a CADTH information specialist using keywords (e.g., feasibility, training, barriers, facilitators) related to implementation. It is likely that an iterative strategy will be followed such that, as we begin to understand important issues and strategies, we will conduct more targeted searches, which may include relevant international published studies, to identify more information on these new and currently unexpected issues.

Eligibility Criteria

We will include English- and French-language reports that describe implementation and context issues, including barriers and facilitators, associated with the use of dental amalgams and composite resins in dental care settings in Canada.

Screening and Selecting Articles for Inclusion

Articles will be screened and selected for inclusion based on the eligibility criteria by one reviewer. First, titles and abstracts will be reviewed to identify potentially relevant papers. Then, the full text of all potentially relevant reports will be retrieved for definitive determination of eligibility.

Data Extraction

Data extraction will be performed by one reviewer. The data will be extracted to a Microsoft Word or Excel spreadsheet and will include bibliographic details of included papers, reported implementation barriers and facilitators, and other key findings related to implementation and relevant context information.

Stage 3: Survey

A survey may be initiated to specifically address gaps in information on implementation issues related to dental amalgams and composite resins in dental care settings in Canada for specific stakeholders. Gaps will be identified through previous stages (consultation and literature search) and may include quantitative data (e.g., utilization data). Specific questions will be developed and a survey will be delivered via email to appropriate respondents.

Analysis

The analysis of data collected from each of the data sources (i.e., consultations, literature, survey) will be performed by two reviewers.

Perspectives

When analyzing data, the items coded and summaries written will be those most relevant at the health services delivery level. The aim will be to provide information to policy-makers regarding relevant contextual factors that influence the use of amalgams and composite resin fillings in Canadian dental practices or programs.

Descriptive Analysis

The findings will be presented in a narrative summary. Where possible, the summary will categorize findings based on the INTEGRATE-HTA categories.[40] INTEGRATE-HTA defines eight domains of context (setting, geographical, epidemiological, socioeconomic, sociocultural, political, legal, and ethical) and four domains of implementation (provider, organization and structure, funding, and policy), each contributing differently to how an intervention is implemented, who can access it, and ultimately the effectiveness of an intervention. CADTH will add a patient domain under the implementation category. Given the emergent nature of this topic area, the planned analysis could be revised based on the data that we collect.

A list and description of factors that have the potential to facilitate or challenge successful implementation will be presented, as well as a summary of potential strategies that could be used to implement or increase the uptake of the technology, if the decision is made to do so. Additionally, a summary of how each factor influences implementation will be provided and, where possible, strategies will be identified that could be used to ensure these factors are taken into consideration or mitigated.

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 dental care system or dental service delivery.

Environmental Assessment

Objective

A comparative assessment of potential environmental effects associated with the use of dental amalgams versus composite resins will take guidance from the Canadian Environmental Assessment Act, 2012[41] and the US Environmental Protection Agency Ecological Risk Assessment framework.[42]

Literature Search

An information specialist will develop a systematic peer-reviewed search strategy for a targeted literature search to identify information on the environmental impact of dental amalgam versus composite resin restorations. In the absence of a globally accepted and suitable definition of the “environment,” we refer to select keywords extracted from Environment and Climate Change Canada’s mandate,[43] namely: natural environment, water, air, soil, flora, fauna, and renewable resources. Relevant synonyms will also be searched (e.g., wildlife for fauna).

Selection Criteria

One reviewer will screen the titles and abstracts of all citations retrieved from the literature search relevant to the research question. For citations that appear eligible for inclusion, the full text of these articles will be retrieved and assessed (by the same reviewer) to determine eligibility. We will focus our search on papers published since 2006, and those based in relevant comparison countries (Canada, US , Australia, New Zealand, UK, and members of the European Economic Area). The clinical use, material composition, and/or environmental impact of amalgam and resins have changed over preceding decades, and thus we limit our search to recent years to focus on the most pertinent literature.

Articles that provide insights into the potential environmental impact associated with dental amalgam and composite resin restorations will be included. For example, the impact may relate to the mercury exposure from dental amalgams and bisphenol A present in composite resins. However, to enable a comparative assessment, we will not restrict our search to papers that examine both amalgams and resins, but will explore 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 may be conducted.

Data Extraction

- From each relevant article, the bibliographic details (authors, year of publication, and country of origin), population and intervention information, and issues related to the environmental impact identified will be captured by one reviewer. The environmental factors will be broken down into variables such as:
  source media (e.g., air, water, soil)
- receptor-macro (flora, fauna)
- receptor-micro (e.g., fish, wildlife, vegetation)
- receptor-specific (list name)
- impact-macro (contamination, effect)
- impact-specific (describe). We will also categorize the findings into key risk assessment criteria, namely hazard identification, exposure assessment, toxicology, and risk characterization.

Content Analysis

The analysis will be conducted in two phases. First, one reviewer will conduct a content analysis to identify issues related to the environmental impact from the use of dental amalgams or composite resins for restorations. The data extracted from the articles will be reviewed, categorized, and organized into themes. An emergent list of codes from the data extracted will be developed, along with a sample text passage that illustrates the application of each code. A constant comparative technique will be applied to identify all instances and appropriateness of the coding framework, and to determine how to expand or merge the codes into themes. The themes derived from the content analysis will be summarized narratively.

Second, in addition to the aforementioned analysis plan, the extracted information will also be organized into the key steps of an ecological risk assessment, namely hazard identification, exposure assessment, toxicology, and risk characterization. This will be done for both amalgams and composites, allowing comparisons to be made.

Protocol Amendments

If amendments to the protocol are required at any time during the study, reasons for changes will be recorded and reported in the final report.

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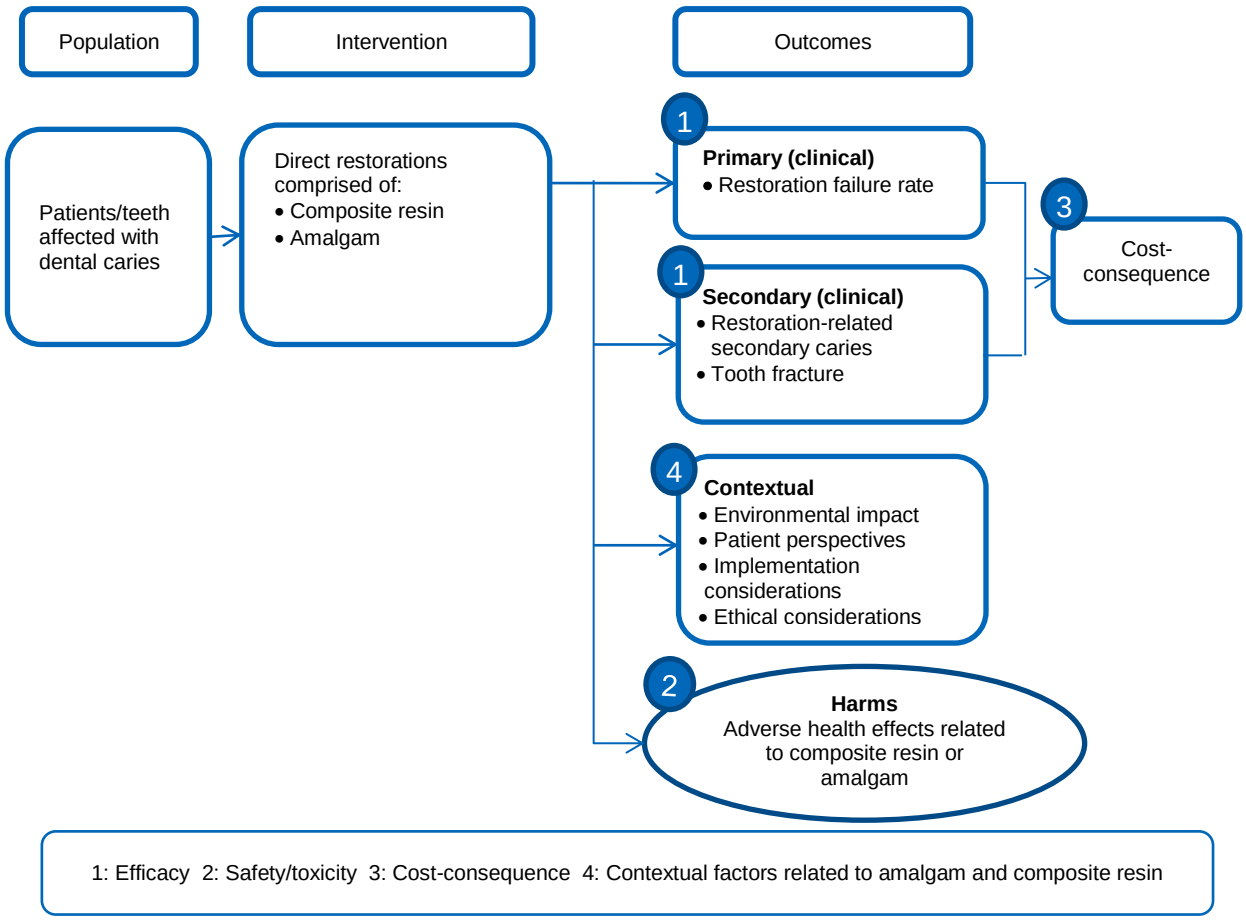
Appendix 1: Analytic Framework

Figure 3: Proposed Analytical Framework – Dental Amalgams Compared with Resin Composites



CADTH

Appendix 2: Literature Search Strategies

Clinical Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to Present MEDLINE Daily and MEDLINE 1946 to Present MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations Cochrane Central Register of Controlled trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	To be completed in June 2017
Alerts:	Monthly search updates until project completion
Study Types:	**Clinical Effectiveness search:** None will be applied **Safety search:** CADTH safety filter
Limits:	Date limit: **Clinical Effectiveness search:** 2012–present Date limit: **Safety search:** none for dental amalgams; 2006–2017 for composite resins Language limit: **Clinical Effectiveness search:** none will be applied Language limit: **Safety search:** none will be applied Conference abstracts: **Clinical Effectiveness search:** will be included Conference abstracts: **Safety search:** will be 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
$ adj	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) Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CCTR)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.jw	Journal title word (MEDLINE, CCTR)
.jx	Journal word (Embase)
.ae	Qualifier (MEDLINE, CCTR); adverse effects Qualifier (Embase); adverse drug reaction

SYNTAX GUIDE	
.tu	Qualifier (MEDLINE, CCTR); therapeutic use
.th	Qualifier (MEDLINE, CCTR); therapy
	Qualifier (Embase); therapy
.ct	Qualifier (MEDLINE, CCTR); contraindications
.po	Qualifier (MEDLINE, CCTR); poisoning
.to	Qualifier (MEDLINE, CCTR); toxicity
	Qualifier (Embase); drug toxicity
.bl	Qualifier (MEDLINE, CCTR); blood
.mo	Qualifier (MEDLINE, CCTR); mortality
.co	Qualifier (MEDLINE, CCTR); complications
.am	Qualifier (Embase); adverse device effect
ppez	Ovid database code; MEDLINE 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

CLINICAL DATABASE SEARCH STRATEGY	
	Q1: Clinical Efficacy
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

CLINICAL DATABASE SEARCH STRATEGY	
	Q1: Clinical Efficacy
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/
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

CLINICAL DATABASE SEARCH STRATEGY	
	Q2: Safety
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.

CLINICAL DATABASE SEARCH STRATEGY	
	Q2: Safety
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/
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

CLINICAL DATABASE SEARCH STRATEGY	
	Q2: Safety
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
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

CLINICAL DATABASE SEARCH STRATEGY	
	Q2: Safety
	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
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

CLINICAL DATABASE SEARCH STRATEGY	
	Q2: Safety
137	125 or 126 or 136
138	116 or 137
139	limit 138 to yr="2006 -Current"
140	84 or 139

OTHER DATABASES		
PubMed	A limited PubMed search was performed 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	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Cochrane Library databases.	
Cochrane Oral Health Group's Trials Register	Same keywords used as per MEDLINE search. Syntax adjusted for Cochrane Oral Health Group's Trials Register.	
LILACs (BIREME Virtual Health Library)	Same MeSH, keywords, and date limits used as per MEDLINE search. Syntax adjusted for LILACs database.	

Grey Literature

Dates for Search:	To be completed in July 2017
Keywords:	
Limits:	Date limit: **Clinical Effectiveness search:** 2012–present Date limit: **Safety search:** none Language limit: **Clinical Effectiveness search:** none Language limit: **Safety search:** 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
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals.

CADTH

Appendix 3: Clinical Studies Full-Text Screening Checklists

Full-Text Screening Checklist Q1

Reviewer: _____ **Date:** _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear**[a]	**No (Exclude)**
1) Population: • Permanent, posterior teeth affected by dental caries	☐	☐	☐
2) Intervention: • Direct composite resin dental restorations	☐	☐	☐
3) Comparators: • Direct amalgam dental restorations	☐	☐	☐
4) Outcomes: • Restoration failure rate	☐	☐	☐
5) Study design: • Randomized controlled trial	☐	☐	☐
Decision for including the study:[b]	Yes ☐		No ☐
Reason(s) for exclusion:	☐ Ineligible study population ☐ Irrelevant intervention ☐ No/irrelevant comparator ☐ Irrelevant outcome(s) ☐ Ineligible study design ☐ Insufficient duration of study follow-up ☐ Ineligible publication format ☐ Other:		

[a] This will be discussed with a second reviewer.

[b] If all items above are answered yes or unclear, then the study will be included.

CADTH

Full-Text Screening Checklist Q2

Reviewer: _____ **Date:** _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear[a]**	**No (Exclude)**
1. Population: • Dental caries patients of any age	☐	☐	☐
2. Intervention: • Composite resin fillings for dental caries	☐	☐	☐
3. Comparators: • Amalgam fillings for dental caries	☐	☐	☐
4. Outcomes: • Primary: injury, toxicity • Secondary: sensitivity, allergic reaction	☐	☐	☐
5. Study designs: • RCTs and non-randomized studies using a comparative design	☐	☐	☐
Decision for including the study:[b]	Yes ☐		No ☐
Reason(s) for exclusion:	☐ Ineligible study population ☐ Irrelevant intervention ☐ No/irrelevant comparator ☐ Irrelevant outcome(s) ☐ Ineligible study design ☐ Ineligible publication format ☐ Other:		

RCT = randomized controlled trial.

[a] This will be discussed with a second reviewer.

[b] If all items above are answered yes or unclear, then the study will be included.

CADTH

Appendix 4: Clinical Studies Data Abstraction Forms

Proposed Data Abstraction Form – Q1

Researcher: _____ **Date:** _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding sources:	

METHODOLOGY	
Study design:	☐ RCT
Subgroup analyses:	
Multivariate analyses:	
Use of a reporting guideline described:	☐ Yes ☐ No

RCT = randomized controlled trial

INTERVENTION(S)/COMPARISON(S)	
Intervention:	
Comparator:	

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Duration of follow-up:	
Loss to follow-up:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Number of included teeth:	
Intervention:	
Comparator:	
Subgroup analyses	
Variable 1	
Variable 2	
(Add variables as needed)	
Outcome	
Multivariate analyses	
Variable1	
Variable 2	
(Add variables as needed)	
Main conclusions:	

Proposed Data Abstraction Form – Q2

Researcher: _____ **Date:** _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding sources:	

METHODOLOGY	
Study design:	☐ RCT ☐ Non-randomized controlled trial ☐ Quasi-experimental study ☐ Controlled before-after study ☐ Cohort study ☐ Case-control study ☐ Other:_____
Subgroup analyses:	
Multivariate analyses:	
Use of a reporting guideline described:	☐ Yes ☐ No

INTERVENTION(S)/COMPARISON(S)	
Intervention:	
Comparator:	

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Duration of follow-up:	
Loss to follow-up:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Number of included patient:	
Age range of patients:	
Intervention:	
Comparator:	
Subgroup analyses	
Variable 1	
Variable 2	
(Add variables as needed)	
Outcome	
Multivariate analyses	
Variable1	
Variable 2	
(Add variables as needed)	
Main conclusions:	

RCT = randomized controlled trial.