CADTH

Integrating Existing Reviews into the CADTH Optimal Use Project on HPV Testing for Primary Cervical Cancer Screening

Rationale for Integrating Existing Reviews

As part of the a priori planned methods for the CADTH Optimal Use Project on HPV Testing for Primary Cervical Cancer Screening, regular literature search alerts and media monitoring are conducted. From this monitoring, several newly published systematic reviews (SRs) or health technology assessments (HTAs) examining the use of HPV (human papillomavirus) testing for cervical cancer screening were identified from May to September 2017. The identification of these potentially relevant and recently published reviews prompted the research team to re-examine clinical systematic review methods in order to identify opportunities to integrate and build on them and therefore not conduct redundant research and not contribute to research waste.

The research team will systematically evaluate whether and how best to integrate existing reviews into this CADTH review through five stages, as outlined in the US Agency for Healthcare Research and Quality (AHRQ) guidance:[1-3]

1. **Locate existing SRs** using a defined and reproducible approach.
2. **Assess the relevance of existing SRs** based on the quality and comprehensiveness of the literature searches; and alignment of the population, intervention, comparators, outcomes, and settings (PICOS) elements with the CADTH review.
3. **Assess the quality of existing SRs** using the AMSTAR 2 critical appraisal tool.
4. **Determine the appropriate use and methods to incorporate existing SRs**, which may involve using one or more complete SR to answer a research question, using selected elements of an existing SR, or not using any existing SRs.
5. **Report methods and results from existing SRs,** which may involve a narrative review or a quantitative review of SR results.

The methods for those evaluations and how decisions will be made at each stage are described in the following sections.

Step 1: Locating Existing Systematic Reviews

In order to identify SRs and meta-analyses, the following keywords will be searched in DistillerSR to assist in rescreening previously retrieved citations, including alerts (as described in the original CADTH review protocol):[4]

> "systematic review" OR "systematic reviews" OR "meta-analysis" OR " meta-analyses" OR "meta analysis" OR "meta analyses" OR "metaanalysis" OR "metaanalyses."

Two reviewers will then independently screen the resulting citations in duplicate to identify SRs. SRs will be those that report an explicit and systematic search, the application of predefined eligibility criteria, and the execution of a risk of bias assessment and the synthesis of results, either narratively or through a meta-analysis.

Step 2: Assessing the Relevance of Existing Systematic Reviews

A number of criteria will be considered in order to assess the relevance of existing SRs to the CADTH work. Relevant reviews are ones that align with the aims of the CADTH review and are able to provide the results required to address both the policy and research questions of interest. Specific issues to be considered include the date of the last literature search, and alignment of PICOS criteria between the existing SRs and the CADTH review.[1-3] All criteria will be assessed independently, in duplicate, by two reviewers. Discrepancies will be resolved through consensus involving other members of the research team, as required.

The relevance of the search strategies of existing reviews will be assessed based on the date cut-off of the most recent literature search update. As per AHRQ guidance,[3] where the search was last updated more than one year ago, the Research Information Specialist will run a search for primary studies that have been published since the earliest literature search cut-off date for each outcome. Any identified primary studies will undergo assessments for relevance to the CADTH research questions according to the same PICOS criteria.

Relevance at the SR level will be categorized into two groups: relevant or irrelevant. Considerations of relevance will first be based on alignment with the a priori CADTH inclusion criteria. A summary of the a priori planned PICOS criteria of the CADTH review[4] are provided in **Error! Reference source not found.** for reference.

Table 1: Abbreviated CADTH PICOS Criteria From the Original Protocol[4]

Population	≥ 21 years or the age of screening initiation in the region
Interventions	All commercially available HPV tests
Comparators	Cytology (LBC or conventional) or other HPV tests with or without triage
Outcomes	• Acceptance of screening • Diagnostic test accuracy • Harms • Referral to colposcopy • Morbidity/mortality • Quality of life
Settings	• Canada • US • Australia • New Zealand • UK • Countries in the European Economic Area

HPV = human papillomavirus; LBC = liquid-based cytology.

To inform the assessment, important study characteristics (e.g., objectives, PICOS criteria, and study design elements [types of and number of studies included, literature search time frames, and quality appraisal tools used and their results]) will be extracted into standardized tables by one reviewer. A second reviewer will verify the extractions. Reviews classified as relevant will have inclusion criteria that exactly match, are broader than, or are included by the PICOS criteria summarized in Table 1. Irrelevant reviews have a different population and intervention, and have differing comparators, outcomes, or country settings, and will be excluded from progressing to the next stage of the evaluation. More than one review may be included for an outcome if the reviews provide different approaches to address the outcome (e.g., different eligible study designs or different methods of synthesizing or presenting results between reviews). If the results of the identified SRs are concordant, the CADTH reviewers will feel confident in the direction and size of the outcomes of interest. If the results of the reviews are discordant, the CADTH reviewers will explore the reasons for these differences and how they may impact certainty in the results. If no reason is uncovered for the discordance, or if no SRs are classified as relevant for an outcome, CADTH will not include existing reviews and will instead continue with the *de novo* systematic review, as planned.

Step 3: Assessing the Quality of Existing Systematic Reviews

A review of the methodological quality of each of the existing and relevant SRs will be done independently by two reviewers using the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) checklist as a guide.[5] Discrepancies will be resolved through discussion, involving a third reviewer, if necessary. Quality scores and overall confidence ratings will not be derived. Instead, the CADTH reviewers will describe the strengths and weaknesses of the SRs as they relate to each domain of the tool, and how they relate to the CADTH reviewers' confidence in the overall quality of the conduct and results of these reviews. These assessments will contribute to considerations of the appropriate use and methods to incorporate existing SRs.

Step 4: Determining the Appropriate Use and Methods to Incorporate Existing Systematic Reviews

The AHRQ guidance[3] recommends four options when determining the appropriate use and methods to incorporate existing SRs into a new review.

These options include:

1. Scan the references of the existing review to compare and quality check the search and inclusion of studies in the new review.
2. Use the search and the included studies of the existing review for data extraction and analysis of the new review.
3. Use the data, bias assessments, and any analyses from the existing review to address the questions of the new review.
4. Use the entirety of the existing review to address the questions of the new review.

If relevant existing reviews are identified, it will then be decided how to appropriately use the reviews and incorporate them into the CADTH review, as laid out in the AHRQ guidance.

Step 5: Reporting Methods and Results from Existing Systematic Reviews

If options 1 or 2 from Step 4 are selected, a meta-analysis may be performed if appropriate, as outlined in the original CADTH protocol.[4] If a meta-analysis is not appropriate, or if options 3 or 4 from Step 4 are selected, a descriptive summary of the characteristics of any included reviews will be developed and included in a final report. Using tables and an accompanying narrative summary, the CADTH reviewers will describe the existing reviews in terms of their objectives, PICOS criteria, and study design elements including the number and types of studies included, literature search criteria, and the quality appraisal tools used. A narrative summary of the results of the quality appraisal for each included review will also be provided. Specifically, detailed summary tables along with a narrative description will be developed to describe assessments of the strengths and limitations of each review to provide the reader with an overview of the quality of the literature. For any primary studies included after the search date of any existing review, descriptive summaries of the study characteristics and quality appraisals using one or more valid and appropriate critical appraisal tools for the study design will be provided, similar to the approach described for SRs.

The outcome-specific and overall results from the SRs will be extracted using a version of the data extraction form from the original CADTH protocol but modified for the SR context. Piloting of the extraction form will be done as described in the original protocol.[4] For outcomes where meta-analysis results are available, the range of individual estimates, pooled estimates, and confidence intervals will be reported when possible. For review results where meta-analysis was not possible, the range of individual estimates will be reported if provided. For any primary studies included after the search date of any existing review, the individual estimates for each outcome will be reported with confidence intervals, where available. All results from both existing reviews and primary studies, if available, will be tabulated, summarized narratively, and presented, by outcome, as they relate to each CADTH research question.

In the case that more than one review addresses an outcome of interest, a matrix of studies included across multiple reviews will be constructed. Information regarding the primary studies included in multiple SRs will be tabulated to illustrate any overlap between reviews, both generally and by outcome. This assessment will be used to guide an analysis of the impact of the results from any one (or more) primary studies on the overall SR results.

Heterogeneity will be explored within and between SRs and the concordance or discordance of existing review results (if more than one review is identified for an outcome) will be examined as a means to assess uncertainty in results across reviews. Where possible, the research team will highlight and discuss any issues of heterogeneity in the primary studies as reported by the review authors. If the CADTH research team identifies any outliers in the analyses or the appearance of heterogeneity in the primary studies that was not adequately addressed by the review authors, the team will examine those primary studies in order to investigate the sources of the observed heterogeneity. Possible sources of heterogeneity that may be expected between primary studies within individual reviews include: the inclusion of different HPV tests, the inclusion of primary studies using different screening or triage strategies, or differences in the ages or vaccination status of the study populations. Sources of potential heterogeneity between reviews are similar to those described for primary studies within reviews but may also result from the inclusion of primary studies with different designs; or result from differences in PICOS or literature search criteria between

reviews, which could then result in the inclusion of a different set of primary studies in the analyses.

Future Action

Newly published SRs and primary studies will continue to be provided to the research team as they are identified through ongoing literature search alerts and media monitoring. Primary studies that have been published since the earliest literature search cut-off for each outcome will undergo assessments for eligibility and relevance to the CADTH research questions, and, if appropriate, will be included in the review as previously outlined.

Newly published SRs identified from the literature search alerts and media monitoring will be assessed against CADTH's inclusion criteria and undergo the relevance and quality assessments described previously. If the review meets the inclusion criteria but does not add to the information that has already been captured through the incorporation of existing reviews and newly published primary studies, it will be briefly summarized in an appendix to the CADTH report. The results may be included in the discussion section, if relevant. If the review does add information that is currently missing from the CADTH review, it will be integrated into the CADTH review, along with any other existing SRs previously identified and assessed through this process. This process will continue, as appropriate, until the stakeholder feedback period has closed.

References

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