

Article Title: The Presence of Complementary and Alternative Medicine Recommendations in Head and Neck Cancer Guidelines: Systematic Review and Quality Assessment

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Abstract

Purpose of review: A high proportion of head and neck cancer (HNC) patients use complementary and alternative medicine (CAM), however, healthcare professionals generally have little knowledge about the safety and efficacy of these therapies. The purpose of this study was to determine the quantity and assess the quality of CAM recommendations across clinical practice guidelines (CPGs) for the treatment and/or management of HNC.

Recent findings: MEDLINE, EMBASE, and CINAHL were systematically searched for HNC CPGs published between 2009 and April 2020; the Guidelines International Network and the National Center for Complementary and Integrative Health websites were also searched. Eligible CPGs containing CAM recommendations were assessed twice with the Appraisal of Guidelines, Research and Evaluation II (AGREE II) instrument, once for the overall CPG and once for the CAM sections. Of 305 unique search results, 7 CPGs mentioned CAM and 4 CPGs made CAM recommendations. The overall CPG scored higher than the CAM section for 4 of 6 domains (overall, CAM): scope and purpose (93.8%, 93.8%), clarity of presentation (88.2%, 64.6%), stakeholder involvement (68.8%, 39.6%), rigor of development (58.3%, 34.6%), editorial independence (42.7%, 42.7%), and applicability (51.6%, 19.8%). Quality varied within and between CPGs.

Summary: Highly scoring CPGs serve as evidence-based resources that clinicians can use to inform their patients about safe and effective CAM use; CPGs achieving variable or lower scores could be improved in future updates based on currently available guideline development/implementation tools. Future research should identify CAM therapies supported by sufficient evidence to be included as part of HNC CPGs.

Background

Head and neck cancers (HNCs) are those characterized by tumours that develop in or around the mouth, nose, throat, larynx, and sinuses and commonly originate in the squamous cell layer, which lines the mucosal surfaces of the oral cavity [1]. HNCs account for 4% of all cancers in the US and this year alone 65,630 Americans are expected to develop HNC. [1]. Worldwide, there are more than 650,000 cases and 330,000 deaths annually, and there exists variation in incidence and anatomic distribution of HNC primarily due to demographic differences in tobacco and alcohol use and human papilloma virus (HPV) infection, which are considered risk factors [2, 3]. The global burden of HNC thus requires the mainstream healthcare system to consider all potential health care interventions for the treatment of HNC, including complementary and alternative medicine (CAM), the use of which continues to increase among cancer patients [2, 4••]. CAM involves using health care approaches that are not usually a part of conventional medicine or may not be associated with typical Western practice. “Complementary” refers to non-mainstream practices used together with conventional medicine, whereas “alternative” refers to non-mainstream practices used in place of conventional medicine. [5]. CAM use in HNC patients has been found to range from 20 to 90%, with dramatic increases in use following a cancer diagnosis [4••, 6].

The most commonly-used CAM therapies for HNC are biologically based therapies such as vitamins and herbal therapies, followed by mind-body interventions such as meditation [6, 7]. Patients may use these therapies to fight the cancer and/or mitigate ill effects from the cancer itself or its treatment [8]. While the scientific evidence regarding the efficacy of a majority of these therapies is limited, a study of CAM use for the treatment of HNC revealed that patients perceived CAM to be beneficial or curative (46.2%), with the remainder finding it neither harmful nor helpful [4••, 6]. Physicians discuss CAM therapies with their HNC patients

minimally [4••, 6, 9]; some HNC patients note that their physicians do not inquire about their CAM use, which may lead to a lack of CAM use disclosure [6, 9]. Even when HNC patients disclose their CAM use, some do not feel satisfied with their physicians response or note that additional information about CAM for HNC is not provided [6, 9]. This discussion is necessary, as it is possible for detrimental interactions to occur between CAM and conventional therapy, of which many patients may be unaware of [7, 9]. Most clinicians, including head and neck oncologists, may find recommending CAM for HNC to be challenging for a number of reasons, including a lack of CAM expertise and/or little information on CAM for HNC due to few clinical trials assessing CAM safety or efficacy regarding disease recurrence, overall survival and quality of life improvement [9]. It is important for health care professionals to seek out and provide objective information, as this also respects their patients' autonomy when they decide to use CAM as a part of their HNC treatment [6].

Healthcare professionals often depend on evidence-based clinical practice guidelines (CPGs) for cancer treatment and/or management recommendations. Transparent methodology, support from systematic reviews, and assessments of the benefits and harms of treatment options in CPGs allow clinicians to make informed and shared health care decisions, resulting in improved patient outcomes [10]. Research on the quality of CPGs for the treatment of HNC is minimal; to our knowledge, only 1 study assessed the quality of oral cancer treatment CPGs and found it to be suboptimal [11••]. In addition, no studies have assessed the quantity or quality of CAM mention and/or recommendations in HNC CPGs. The purpose of this study was thus to conduct a systematic review to determine the quantity of CAM mention in HNC treatment and/or management CPGs for adults and assess the quality of CAM recommendations using the AGREE II instrument.

Methods

Approach

A systematic review was conducted to identify HNC CPGs using standard methods [12] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [13]. A protocol was registered with PROSPERO, registered number CRD42020182231. Eligible CPGs were assessed with the widely-used and validated Appraisal of Guidelines for Research & Evaluation Instrument (AGREE II) instrument [14]. Articles with CAM recommendations were re-assessed with AGREE II whereby the assessors applied the 23 items to only the CAM sections of the CPG. AGREE II consists of 23 items grouped in domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence.

Eligibility Criteria

Eligibility criteria for HNC CPGs were based on the Population, Intervention, Comparison, and Outcomes framework. Eligible populations were adults aged 19 years and older with HNC. With respect to interventions, we only included CPGs that provided recommendations for the treatment and/or management of HNC in order to determine whether any mention or recommendations of CAM therapies were present. Comparisons pertained to the assessed quality of HNC CPGs. Outcomes were AGREE II scores which reflect CPG content and format. The following conditions were also applied to define eligible CPGs: developed by non-profit organizations including academic institutions, government agencies, disease-specific foundations, or professional associations or societies; published in 2009 or later; English language; and either publicly available or could be ordered through our library system. Publications in the form of consensus statements, protocols, abstracts, conference proceedings, letters or editorials; based on primary studies that evaluated HNC management

or treatment; or focused on HNC curriculum, education, training, research, professional certification, or performance were not eligible. It should be noted that only eligible CPGs that contained CAM therapy recommendations were assessed using the AGREE II tool, in order to determine the difference in AGREE II scores between the overall CPG and specifically the CAM sections; only demographic information is reported for eligible CPGs that did not contain CAM therapy recommendations.

Searching and Screening

MEDLINE, EMBASE, and CINAHL were searched on April 17th, 2020, from 2009 to April 16th, 2020 inclusive. The search strategy (Supplementary File 1) included Medical Subject Headings and keywords that reflect terms commonly used in the literature to refer to HNC. We also searched the Guidelines International Network, a repository of guidelines [<https://www.g-i-n.net/>] using keyword searches restricted based on the eligibility criteria including “head and neck cancer” and “head and neck neoplasms”, and the National Center for Complementary and Integrative Health (NCCIH) website which contained a single list of CAM guidelines [<https://nccih.nih.gov/health/providers/clinicalpractice.htm>]. ED and another research assistant screened titles and abstracts, as well as potentially includable full-text items to confirm eligibility. JYN reviewed the screened titles and abstracts and full-text items to standardize screening and helped to discuss and resolve selection differences between the 2 screeners.

Data Extraction and Analysis

The following data were extracted from each CPG and summarized: CPG title, authors; year of publication; country of first author; guideline-publishing organization (academic institutions, government agencies, disease-specific foundations, or professional associations

or societies); and whether any CAM was mentioned in the CPG. Provided CAM was mentioned in the CPG, the types of CAM therapies, CAM recommendations, CAM funding sources, and CAM providers that were part of the guideline panel were also data extracted. To assess applicability, the website of each developer was searched for any additional knowledge-based resources in support of implementation.

CPG Quality Assessment

Eligible guidelines containing CAM recommendations were assessed with the AGREE II instrument based on standardized methods [14]. A pilot test was first conducted with 3 sample CPGs, where ED, JYN, and the other research assistant independently assessed these CPGs with the AGREE II instrument. All three assessors met to resolve discrepancies by discussion to standardize the use of the AGREE II instrument. All eligible CPGs containing CAM therapy recommendations were then independently assessed by ED and the other research assistant, with JYN resolving differences. Specifically, 23 items across 6 domains were assessed using a 7-point Likert scale from strongly disagree (1) to strongly agree (7) that the CPG fulfils a given item. Each item assessment was performed twice per CPG: once for the overall CPG, and once for the CAM-specific sections. The AGREE II questions used for the scoring of the CAM sections were slightly modified and are found in Supplementary File 2. Next, an overall quality assessment of both the overall CPG and CAM-specific section of each CPG was conducted by ED and the other research assistant, with a recommendation for or against the use of each CPG, informed by this assessment. The average of all scores scored by 1 appraiser for the 23 items in a CPG (the overall and CAM sections scored separately) was calculated; the average appraisal score was then calculated by taking the average of this value for both appraisers. The average overall assessment was created by taking the average of the “overall assessment” of a CPG (the overall and CAM sections

assessed separately) for both appraisers. Scaled domain percentages were generated by taking the sum of all item scores for both appraisers within each domain, scaling by maximum and minimum possible domain scores and turning this into a percentage. Domains were then compared based on these percentages. For both the overall and CAM sections of each CPG, average appraisal scores, average overall assessments, and scaled domain percentages were tabulated.

Results

Search Results (Fig. 1)

Searches retrieved 412 items, 305 were unique, and 242 titles and abstracts were eliminated, leaving 63 full-text CPGs that were considered. Of those, 15 were not eligible because they were reviews (n = 6), did not address HNC treatment (n = 4), guideline summaries (n = 2), were consensus-based CPGs (n = 1), not specific to HNC (n = 1), were irretrievable (n = 1), leaving 48 CPGs eligible for review. Of these CPGs, 7 out of the 48 made mention of CAM therapies and 4 made CAM therapy recommendations.

CPG Characteristics (Tables 1 and 2)

Eligible CPGs were published from 2010 to 2020 in the UK (n = 20), US (n = 13), France (n = 5), Spain (n = 3), Belgium (n = 2), Australia (n = 1), Canada (n = 1), China (n = 1), Malaysia (n = 1), and Switzerland (n = 1). The CPGs were funded and/or developed by professional associations or societies (n = 26), the UK Multidisciplinary Guidelines (n = 19), government agencies (n = 2), and an academic agency (n = 1). Seven CPGs made mention of CAMs [15,16,17,18,19,20,21] (Table 1). These CAMs included nutritional supplements (n = 3), acupuncture (n = 2), aromatherapy (n = 2), aerobic exercise (n = 1), biofeedback (n = 1), guided imagery (n = 1), massage therapy (n = 1), physiotherapy (n = 1),

auriculotherapy (n = 1), and homoeopathy (n = 1). Recommendations relating to CAM were made in 4 of these 7 CPGs and were associated with nutritional supplements (n = 2), aerobic exercise (n = 1) along with aromatherapy and massage therapy (n = 1); only these CPGs were assessed using the AGREE II instrument. No CAM funding sources were found across any of the CPGs, and none of the CPGs included CAM providers as part of the guideline panel. We provide a summary of CAM recommendations made across HNC CPGs for the benefit of clinicians and researchers in Fig. 2. In addition, all eligible CPGs that did not make mention of CAM or provide CAM recommendations (n = 41) are provided in Table 2.

CPG Mentioning CAM Without Recommendations

Of the 7 CPGs that mentioned CAM, 2 did not provide recommendations, while 1 did provide recommendations. However, the title of this CPG included “short version” with no full-length version found publicly or in the library system and therefore it was not assessed due to the possibility of missing information [20]. The CAM data mentioned in these 3 CPGs were extracted, but not assessed with the AGREE II instrument. In these CPGs, CAM was briefly and vaguely mentioned, usually at the end of a list of interventions to use for specific physical effects that result from HNC, namely sleep disturbance/apnea, early pain, and xerostomia (from radiotherapy), [18, 20, 21].

Average Appraisal Scores, Average Overall Assessments, and Recommendations

Regarding Use of CPGs: Overall CPG (Table 3)

Average appraisal scores, average overall assessments, and recommendation regarding use for each overall CPG are shown in Table 3. The average appraisal scores for each of the 4 CPG ranged from 4.0 to 6.2 on the 7-point Likert scale (where 7 equals strongly agree that the item is met); 2 CPGs exceeded an average appraisal score of 5.0 [15, 16]. Average overall

assessments for the 4 CPGs ranged between 4.0 (lowest) and 5.5 (highest), including 2 CPGs exceeding a score of 5.0 [15, 16].

Average Appraisal Scores, Average Overall Assessments, and Recommendations Regarding Use of CPGs: CAM Sections (Table 3)

Average appraisal scores, average overall assessments, and recommendation regarding use for the CAM section of each CPG are shown in Table 3. The average appraisal scores for each of the 4 CPGs ranged from 3.0 to 4.2 on the 7-point Likert scale (where 7 equals strongly agree that the item is met); 2 CPGs achieved or exceeded an average appraisal score of 4.0 [15, 16]. Average overall assessments for the 4 CPGs ranged between 2.5 (lowest) and 4.0 (highest), including 1 CPG equalling a score of 4.0 [19].

Overall Recommendations: Overall CPG (Table 4)

None of the 4 overall CPGs were recommended by both appraisers. Appraisers agreed in their overall recommendation for 3 of 4 CPGs including 3 Yes with modifications [15, 17, 19]. The remaining CPG was rated at Yes and Yes with modifications [16].

Overall Recommendations: CAM Sections (Table 4)

None of the 4 CAM sections were recommended by both appraisers. Appraisers agreed in their overall recommendation for all CPGs including 1 No [17], and 3 Yes with modifications [15, 16, 19].

Scaled Domain Percentage Quality Assessment (Table 5)

With respect to scaled domain percentages of the overall CPG, scope and purpose scores ranged from 83.3% to 100.0%, stakeholder involvement scores were 52.8% to 86.1%, rigor-of-development scores were 33.3% to 82.3%, clarity of presentation scores ranged from

83.3% to 94.4%, applicability scores were 35.4% to 83.3%, and editorial independence scores ranged from 4.2% to 83.3%. With respect to scaled domain percentages of the CAM sections, scope and purpose scores ranged from 86.1% to 100.0%, stakeholder involvement scores were 33.3% to 44.4%, rigor of development scores were 19.8% to 45.8%, clarity of presentation scores ranged from 52.8% to 75.0%, applicability scores were 2.1% to 35.4%, and editorial independence scores ranged from 4.2% to 83.3%.

Scope and Purpose

Generally, the overall objectives, health questions covered, and target population were well covered by all 4 CPGs, both overall and for the CAM sections. Authors provided the goal of the CPG, health intent, interventions, and outcomes. The target population was described as patients and/or adults with HNC at minimum. The scope and purpose of the overall CPG were similar to their respective CAM sections, as the CPGs aimed to provide recommendations on the multidisciplinary care of patients with HNC [15,16,17, 19].

Stakeholder Involvement

Regarding the guideline development group of the overall CPGs, all 4 discussed institutional affiliations, while only 2 mentioned some of the following: degrees held by, institutional affiliation, geographical location, subject discipline, and guideline development role of each member [15, 16]. None of the CPGs contained CAM experts. None of the CPGs explicitly detailed the views and preferences of the target population for both overall and the CAM sections, but all 4 acknowledged that patients have unmet needs regarding diverse care [15,16,17, 19]. The target users of the CPG were well defined for both the overall CPG and the CAM section of all 4 CPGs; a variety of practicing clinicians were mentioned, including

palliative and/or supportive care practitioners [15, 17], and allied health professionals such as dietitians [15, 16, 19].

Rigor of Development

Systematic methods and the criteria for selecting evidence were only present in 2 CPGs; however, these only pertained to the overall CPG, as the CAM sections were generally limited in these areas [15, 16]. The other 2 CPGs did not use systematic methods or present criteria for selecting evidence at all [17, 19]. With respect to overall CPGs, the strengths and limitations of the body of evidence were somewhat clearly described for 3 CPGs [15, 16, 19], but not for 1 CPG [17]; in contrast, these were all not clearly described in the CAM sections of all CPGs. The methods for formulating the recommendations were provided in detail for 2 CPGs [15, 16] whereas the others provided fewer information [17, 19]; these methods were generally consistent between the overall CPG and the CAM section for all 4 CPGs. For all 4 CPGs, the health benefits, side effects, and/or risks were largely addressed overall [15,16,17, 19]. The CAM sections for these aspects scored similarly as the overall for 2 CPGs [17, 19] while the other 2 provided minimal information [15, 16]. All 4 CPGs provided an explicit link between their recommendations and the supporting evidence overall and 3 of these CPGs provided this at a nearly similar degree within their CAM sections, with the exception of 1, in which this section scored lower [17]. All 4 CPGs explicitly stated they were externally reviewed by experts prior to publication but only 2 provided a description of the reviewers [15, 16] while only 1 provided the intent of the external review [16]. None of the CPGs were externally reviewed by CAM experts. Two CPGs included a procedure for updating the guideline [15, 16] while the other 2 did not [17, 19]; this applied to both the overall and CAM section of the CPG.

Clarity of Presentation

All CPGs generally offered specific and unambiguous recommendations overall, where many if not all of the following were mentioned to some degree: statement of the recommended action, the intent of the recommended action, the relevant population, and caveats [15,16,17, 19]. However, only 1 CPG maintained this in their CAM section [15], while the others scored lower on this aspect in this section [16, 17, 19]. All 4 CPGs presented different options for the treatment and/or management of HNC overall, with this score being slightly lower for the CAM section in 3 CPGs [16, 17, 19], and notably lower in 1 [15]. Key recommendations were easily identifiable for all 4 CPGs, both overall and in the CAM sections [15,16,17, 19].

Applicability

The description of facilitators and barriers to guideline application was inconsistent; 3 CPGs scored in the middle of the 7-point scale for applicability domain items for the overall CPGs [15, 17, 19], with 1 scoring higher [16]. The CAM section for 3 of the 4 CPGs was less thorough when compared to the overall [15,16,17] while 1 CAM section was slightly more thorough [19]. The CPGs included few [17], some [19] and extensive [15, 16] advice and/or tools for the implementation of the recommendations overall, while the CAM section provided fewer advice and/or tools for CPG implementation in comparison [15, 17, 19], with the exception of 1 that scored close to the overall [16]. Only 1 CPG considered the potential resource implications of applying the recommendations, and this was addressed overall and not in the CAM section [16]. Monitoring and auditing criteria were well-defined for 2 CPGs overall [16, 19]; the other 2 contained less of these criteria [15, 17]. The CAM sections of 1 CPG contained somewhat fewer of this aspect than the overall CPG [19], while the others contained very little or none at all [15,16,17].

Editorial Independence

CPGs varied with respect to the reporting of the funding source or competing interests of the members of the guideline development panel. Two CPGs did not declare whether funding sources influenced the content of the guideline, nor did they report whether any competing interests existed. [17, 19]. One CPG clearly addressed both aspects; the authors disclosed that they were supported financially and described the type of competing interest considered [16]. The other CPG did not explicitly address funding but did address competing interests both by describing the types of competing interests considered and how they were identified [15]. However, these 2 CPGs did not specify how any potential competing interests may have influenced the guideline development process or the issuing of recommendations [15, 16].

Discussion

As identifying credible, evidence-based clinical practice recommendations allows healthcare professionals to make well-informed decisions, alongside their patients, regarding the use of CAM therapies for HNC, the purpose of the present study was to determine the quantity of CAM mention and assess the quality of CAM recommendations across CPGs for the treatment and/or management of HNC. This study identified 48 CPGs published between 2010 and 2020 that discussed the treatment and/or management of HNC, of which 7 CPGs made mention of CAM, and 4 CPGs made CAM therapy recommendations. As assessed by the 23-item AGREE II instrument, domain quality varied within and between the overall and CAM sections of individual CPGs, as well as across different CPGs (1 = strongly disagree, 7 = strongly agree that criteria are met). With respect to the assessment of the overall CPG, 2 CPGs scored 5.0 or higher in both average appraisal score and average overall assessment [15, 16], and the other 2 CPGs scored 5.0 or lower in both of these metrics [17, 19]. With respect to the assessment of the CAM section of each CPG, all CPGs scored 4.0 or lower in

both average appraisal score and average overall assessment, with the exception of the average appraisal score of 1 CAM section, which received a 4.2 [16].

To our knowledge, this is the first study to identify the quantity and assess the quality of CAM recommendations in CPGs providing recommendations the treatment and/or management of HNC. In this study, the scaled domain percentages for the overall CPGs from the highest to lowest were as follows: scope and purpose (93.8%), clarity of presentation (88.2%), stakeholder involvement (68.8%), rigor of development (58.3%), applicability (51.6%), and editorial independence (42.7%). The scaled domain percentages for the CAM section of the CPGs from the highest to lowest were as follows: scope and purpose (93.8%), clarity of presentation (64.6%), editorial independence (42.7%), stakeholder involvement (39.6%), rigor of development (34.6%), and applicability (19.8%). The findings are similar to those in studies assessing CPGs on other clinical topics. In a previous study identifying complementary and integrative medicine (CIM) recommendations in lung cancer CPGs, the scaled domain percentages were ordered in a similar fashion from the highest (scope and purpose 82.4% overall, 76.9% CIM) to lowest (applicability 29.9% overall, 18.8% CIM) with the CIM sections scoring the same as or lower than the overall CPG in all domains [22]. In another study assessing CAM recommendation quality across cancer-related pain CPGs, a similar scaled domain percentage order was found whereby the scope and purpose domain scored highest (88.1% overall, 88.1% CAM section) and the applicability domain scored lowest (21.0% overall, 8.5% CAM section) [23]. Additionally, no CAM recommendations were found across colon cancer or ovarian cancer clinical practice guidelines [24, 25]. These findings were also similar for the quality of CAM in low back pain CPGs, where scope and purpose scored 88.6% overall, 87.1% for the CAM sections and applicability scored 31.8% overall and 21.8% for the CAM sections [26]. Furthermore, previous studies that assessed

oral cancer treatment and CAM-related CPGs also reported a similar order of domain percentages [11, 27]. Therefore, the variable and sub-optimal quality of domains within individual CPGs as well as the CAM section in relation to the overall CPG is not a unique finding.

The present study revealed that few of these CPGs refer to CAM for the treatment and/or management of HNC. As up to at least 1 in 5 HNC patients use CAM, it is imperative that healthcare professionals have access sufficient evidence-based resources to inform patients about the safe and effective use of CAM therapies [4, 7,8,9, 28]. This study also revealed that the quality of HNC CPGs that make recommendations of CAM varied; there were differences across domains within the overall and CAM sections of a CPG, between the overall and CAM sections, and across independent CPGs. In general, the CAM recommendations were less thorough than the recommendations of the CPG as a whole. This finding is relevant to existing and future HNC CPG developers, who may improve and/or create CPGs in a manner that addresses the aforementioned discrepancies in CAM quantity and quality. There exists a plethora of guideline development tools to inform the creation of high-quality CPGs [29,28,29,30,31,34].

Strengths and Limitations

This study is strengthened by the use of a comprehensive systematic review method to identify eligible CPGs for the treatment and/or management HNC, along with the assessment of their quality by means of a validated AGREE II instrument, an internationally accepted gold standard for guideline appraisal [14]. The limitations of this study may include the fact that CPGs were independently assessed by 2 appraisers, while 4 appraisers are recommended by the AGREE II instrument to enhance reliability. To mitigate this and standardize scoring,

JYN, ED, and the other research assistant initially conducted a pilot test where they appraised 3 independent CPGs, followed by a discussion of the results to reach consensus on how to apply the AGREE II instrument. Subsequent to the appraisal of the 4 CPGs that make CAM therapy recommendations, JYN, ED, and the additional research assistant discussed and resolved any uncertainties in a manner that did not modify legitimate discrepancies. In addition, all CPGs that included CAM therapy recommendations for HNC may not have been identified because, to establish a feasible scope, we did not search for CPGs on clinical topics outside of HNC (i.e., general cancer CPGs) and examine them for CAM-related content.

Conclusions

This study identified 4 HNC CPGs published since 2016 that contained CAM therapy recommendations including nutritional supplements, aerobic exercise, aromatherapy, and massage therapy. Appraisal of these CPGs with the AGREE II instrument revealed that quality varied within and between the overall and CAM sections of the CPGs, as well as across CPGs. CPGs that scored higher with AGREE II and were assessed favourably by appraisers may serve as a starting point for shared decision-making between patients and health care professionals with regard to CAM therapy use for HNC treatment and/or management. CPGs that achieved variable or lower scores for some or all of these metrics can be updated and improved according to AGREE II specifications along with the numerous resources available for guideline development and implementation. Overall, few HNC CPGs that make mention or recommend CAM have been published, thus limiting the access health care professionals and researchers have to evidence-based resources necessary for informed and shared decision-making. A lack of professional guidance may result in HNC patients misusing CAM therapies. Thus, additional research on the safety and effectiveness of

promising CAM therapies for the treatment and/or management of HNC is needed to serve as the basis for future HNC CPG development.

Data Availability

All relevant data are included in this manuscript.

Abbreviations

AGREE II: Appraisal of Guidelines for Research & Evaluation II

CAM: complementary and alternative medicine

CIM: complementary and integrative medicine

CPG: clinical practice guideline

HNC: head and neck cancer

NCCIH: National Center for Complementary and Integrative Health

PICO: Patients, Intervention, Comparison and Outcomes

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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treatment and/or management of lung cancer. Finding very few recommendations overall, this study highlights a major knowledge gap, which may hinder informed shared-decision making between practitioner and provider regarding safe and effective CAM use, especially provided that most healthcare practitioners in oncology have little to no training in this topic area.

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manipulation: systematic review and assessment using AGREE II. *BMC Complement Altern Med.* 2016;16(425):1.

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Contributions

JYN: designed and conceptualized the study, collected and analysed data, co-drafted the manuscript, and gave final approval of the version to be published.

ED: assisted with the collection and analysis of data, co-drafted the manuscript, and gave final approval of the version to be published.

Ethics declarations

Ethics Approval and Consent to Participate

This study involved a systematic review of peer-reviewed literature only; it did not require ethics approval or consent to participate.

Consent for Publication

All authors consent to this manuscript's publication.

Competing Interests

The authors declare that they have no competing interests.

Supplementary Information

Supplementary File 1: MEDLINE Search Strategy for HNC CPGs Executed April 17th, 2020

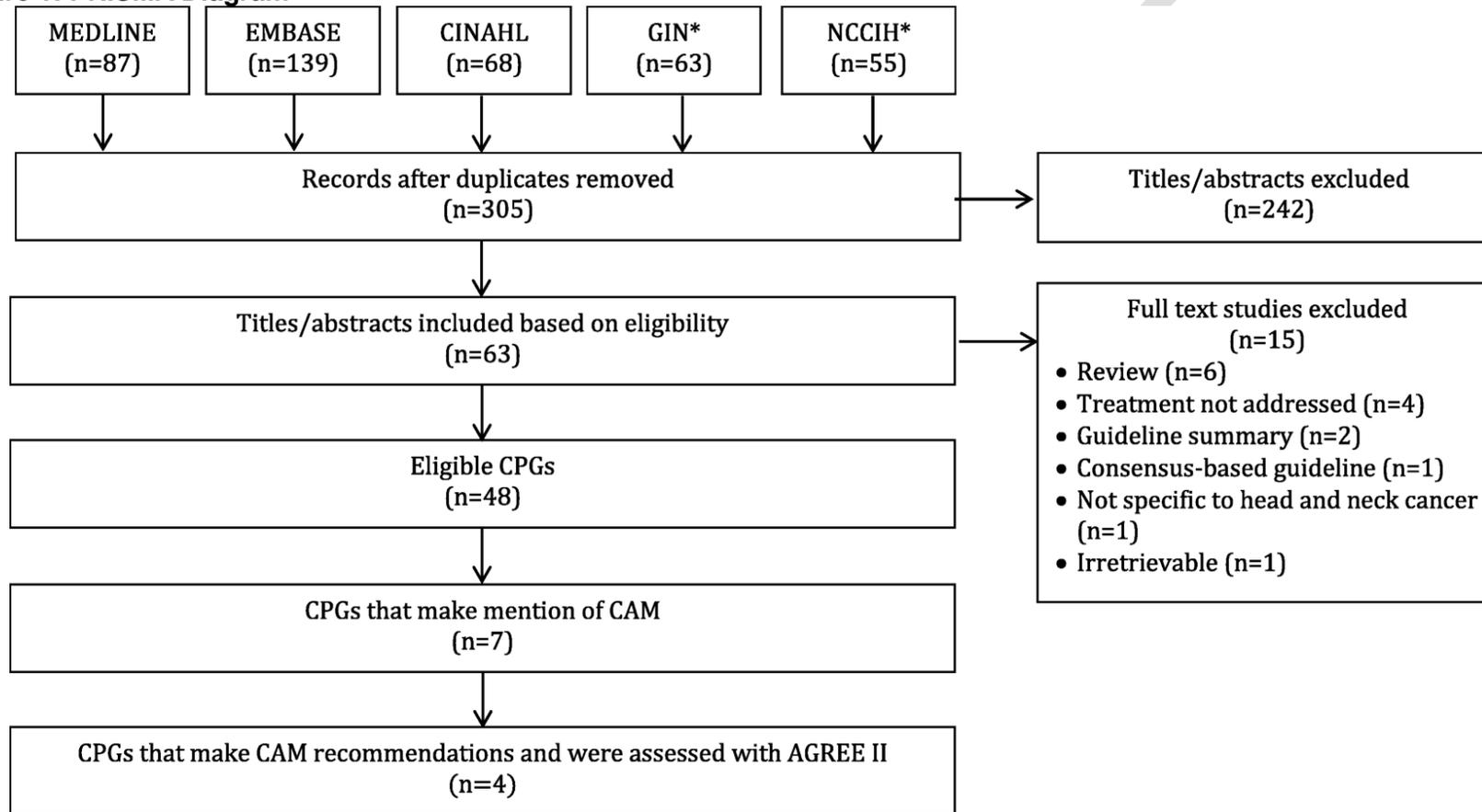
Supplementary File 2: Modified AGREE II Questions Used to Guide Scoring of CAM

Sections of Each CPG.

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Figures

Figure 1: PRISMA Diagram



*List of Abbreviations: CAM = complementary and alternative medicine, CPG = clinical practice guideline, GIN = Guidelines International Network, NCCIH = National Center for Complementary and Integrative Health

Figure 2: Summary of CAM Recommendations in CPGs

CPG	CAM Therapy			
	Aerobic exercise	Aromatherapy	Massage therapy	Nutritional supplements
Nekhlyudov 2017 [15]	+	N/A	N/A	N/A
Choo 2016 [16]	N/A	N/A	N/A	+
Cocks 2016 [17]	N/A	0	0	N/A
Talwar 2016 [19]	N/A	N/A	N/A	+

Legend:
 +/green = recommendation for the therapy's use
 -/red = recommendation against the therapy's use
 0/yellow = recommendation unclear/uncertain/conflicting
 N/A/grey = no recommendation provided

Tables

Table 1: Characteristics of Eligible CPGs with CAM Therapy Mention and/or Recommendations

CPG	Country (first author)	Developer	CAM category	Guideline topic
Nekhlyudov 2017 [15]	US	American Society of Clinical Oncology	Aerobic Exercise	HNC survivorship care
Choo 2016 [16]	Malaysia	Malaysia Health Technology Assessment Section	Nutritional supplements	Management of nasopharyngeal carcinoma
Cocks 2016 [17]	UK	UK National Multidisciplinary Guidelines*	Massage therapy and aromatherapy, nutritional supplements	Palliative and supportive care in HNC
Cohen 2016 [18]	US	American Cancer Society	Aromatherapy, guided imagery and biofeedback	HNC survivorship care
Talwar 2016 [19]	UK	UK National Multidisciplinary Guidelines*	Nutritional supplements	Nutritional management in HNC
Cuny 2015 [20]	France	French Otorhinolaryngology–Head and Neck Surgery Society	Physiotherapy, auriculotherapy, acupuncture and homoeopathy	Care pathway organization in HNC
Pfister 2011 [21]	US	National Comprehensive Cancer Network	Acupuncture	HNC treatment

1. *Endorsed by British Association of Endocrine and thyroid Surgeons (BAETS), British Association of Head and Neck Oncologists (BAHNO), British Association of Oral and Maxillofacial Surgeons (BAOMS), British Association of

Otorhinolaryngology-Head and Neck Surgery (ENT UK), British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS), The Royal College of Pathologists (RCPath), and The Royal College of Radiologists (Faculty of Clinical Oncology) (RCR)

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Table 2: Eligible CPGs with no CAM Therapy Mention or Recommendations

CPG citation	Country (first author)	CPG topic
Maghami E, Ismaila N, Alvarez A, Chernock R, Duvvuri U, Geiger J, Gross N, Haughey B, Paul D, Rodriguez C, et al. Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline. <i>J Clin Oncol.</i> 2020;38:1–29.	US	Diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck
Biau J, Dunet V, Lapeyre M, Simon C, Ozsahin M, Gregoire V, Bourhis J. Practical clinical guidelines for contouring the trigeminal nerve (V) and its branches in head and neck cancers. <i>Radiother Oncol.</i> 2019;131:192–201.	Switzerland	Contouring the trigeminal nerve and its branches in HNC
Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for head and neck cancer working group. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for head and neck cancer 2018 (English version). <i>Chin J Cancer Res.</i> 2019;31(1):84–98.	China	HNC diagnosis and treatment
Koyfman SA, Ismaila N, Crook D, D’Cruz A, Rodriguez CP, Sher DJ, Silbermins D, Sturgis EM, Tsue TT, Weiss J. Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline. <i>J Clin Oncol.</i> 2019;37(2):1753–1776.	US	Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx
Iglesias Docampo LC, Arrazubi Arrula V, Baste Rotllan N, Carral Maseda A, Cirauqui Cirauqui B, Escobar Y, Lambea Sorrosal JJ, Padtor Borgonon M, Rueda A, Cruz Hernandez JJ. SEOM clinical guidelines for the treatment of head and neck cancer (2017). <i>Clin Transl Oncol.</i> 2018;20:75–83.	Spain	HNC treatment

CPG citation	Country (first author)	CPG topic
Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, Burtness B, Busse PM, Caudell JJ, Cmelak AJ et al. Head and Neck Cancers, Version 2.2017. J Natl Compr Canc Netw. 2017;15(6):761–770.	US	HNC treatment
Forastiere AA, Ismaila N, Lewin JS, Nathan CA, Adelstein DJ, Eisbruch A, Fass G, Fisher SG, Laurie SA, Le Q-T et al. Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;36(11):1143–1169.	US	Use of larynx-preservation strategies in the treatment of laryngeal cancer
Quon H, Vapiwala N, Forastiere A, Kennedy EB, Adelstein DJ, Boykin H, Califano JA, Holsinger C, Nussenbaum B, Rosenthal DI, et al. Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2017;35(36):4078–4090.	US	Radiation therapy for oropharyngeal squamous cell carcinoma
Sher DJ, Adelstein DJ, Bajaj GK, Brizel DM, Cohen EE, Halthore A, Harrison LB, Lu C, Moeller BJ, Quon H et al. Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma: An ASTRO Evidence Based Clinical Practice Guideline. Prac Rad Oncol. 2017;7:246–253.	US	Radiation therapy for oropharyngeal squamous cell carcinoma
Winkvist E, Agbassi C, Meyers BM, Yoo J, Chan KKW, Head and Neck Disease Site Group. Systemic therapy in the curative treatment of head-and-neck squamous cell cancer: Cancer Care Ontario clinical practice guideline. Curr Oncol. 2017;24(2):e157-e162.	Canada	Systemic therapy for treatment of head and neck squamous cell cancer
Ahmed OA, Kelly C. Head and neck melanoma (excluding ocular melanoma): UK National	UK	Head and neck

CPG citation	Country (first author)	CPG topic
Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S133–S141.		melanoma
Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/NG36 . 2016. Accessed 27 Jun 2020.	UK	Assessment and management of cancer of the upper aerodigestive tract
Homer JJ, Lesser T, Moffat D, Slevin N, Price R, Blackburn T. Management of lateral skull base cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S119–S124.	UK	Management of lateral skull base cancer
Homer JJ. Surgery in head and neck cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S68-S70.	UK	Surgery in HNC
Humphris G. Psychological management for head and neck cancer patients: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S45-S48.	UK	Psychological management of HNC
Jones TM, De M, Foran B, Harrington K, Mortimore S. Laryngeal cancer: UK National Multidisciplinary guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S75-S82.	UK	Laryngeal cancer treatment
Kerawala C, Roques T, Jeannon J-P, Bisase B. Oral cavity and lip cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S83-S89.	UK	Oral cavity and lip cancer treatment
Lund VJ, Clarke PM, Swift AC, McGarry GW, Kerawala C, Carnell D. Nose and paranasal sinus tumours: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S111–118.	UK	Treatment of nose and paranasal sinus tumours

CPG citation	Country (first author)	CPG topic
Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2): S170-S175.	UK	Investigation and management of the unknown primary with metastatic neck disease
Mehanna H, Evans M, Beasley M, Chatterjee S, Dilkes M, Homer J, O'Hara J, Robinson M, Shaw R, Sloan P. Oropharyngeal cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S90-S96.	UK	Oropharyngeal cancer treatment
Mehanna H, Kong A, Ahmed SK. Recurrent head and neck cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S181-S190.	UK	Recurrent HNC
Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S150-S160.	UK	Management of thyroid cancer
Nutting C. Radiotherapy in head and neck cancer management: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. S2):S66-S67.	UK	Radiotherapy in HNC management
Paleri V, Urbano TG, Mehanna H, Repanos C, Lancaster J, Roques T, Patel M, Sen M. Management of neck metastases in head and neck cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S161-S169.	UK	Management of neck metastases in HNC
Pracy P, Loughran S, Good J, Parmar S, Goranova R. Hypopharyngeal cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S104-S110.	UK	Hypopharyngeal cancer treatment
Simo R, Homer J, Clarke P, Mackenzie K, Paleri V, Pracy P, Roland N. Follow-up after	UK	Follow-up after HNC

CPG citation	Country (first author)	CPG topic
treatment for head and neck cancer: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S208-S211.		treatment
Simo R, Robinson M, Lei M, Sibtain A, Hickey S. Nasopharyngeal carcinoma: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. 2):S97-S103.	UK	Nasopharyngeal carcinoma treatment
Sood S, McGurk M, Vaz F. Management of Salivary Gland Tumours: UK National Multidisciplinary Guidelines. J Laryngol Otol. 2016;130 (Suppl. S2):S142-S149.	UK	Management of salivary gland tumours
Deneuve S, Babin E, Lacau-St-Guilly J, Baujat B, Bensadoun R-J, Bozec A, Chevalier D, Choussy O, Cuny F, Fakhry N et al. Guidelines (short version) of the French Otorhinolaryngology – Head and Neck Surgery Society (SFORL) on patient pathway organization in ENT: The therapeutic decision-making process. Early management of head and neck cancer. Eur Ann Otorhinolaryngol Head Neck Dis. 2015;132:213–215	France	Early management of HNC
Pavillet J, Guigay J, Lacau Saint-Guily J, Righini C-A. Organization of primary care pathway in head and neck oncology (short version): Organization of chemotherapy in head and neck oncology. Eur Ann Otorhinolaryngol Head Neck Dis. 2015;132:209–212.	France	Organization of chemotherapy in HNC
Pfister DG, Spencer S, Brizel DM, Burtness B, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW et al. Head and Neck Cancers, Version 1.2015. J Natl Compr Canc Netw. 2015;13(7):847–856.	US	HNC treatment
Whiteman DC, Appleyard M, Bahin FF, Bobryshev YV, Bourke MJ, Brown I, Chung A, Clouston A, Dickins E, Emery J, et al. Australian clinical practice guidelines for the diagnosis and management of Barrett’s oesophagus and early oesophageal adenocarcinoma. J	Australia	Diagnosis and management of Barrett’s oesophagus and early

CPG citation	Country (first author)	CPG topic
Gastroenterol Hepatol. 2015;30:804–820.		oesophageal adenocarcinoma
Bejar C, Basset-Seguín N, Faure F, Fieschi C, Frances C, Guenne C, Lebbe C, Peraldi MN, Roux J, Lamas G et al. French ENT Society (SFORL) guidelines for the management of immunodeficient patients with head and neck cancer of cutaneous origin. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131:121–129.	France	Management of immunodeficient patients with HNC of cutaneous origin
Durbec M, Couloigner V, Tronche S, Albert S, Kanitakis J, Ltaief Boudrigua A, Malard O, Maubec E, Mourrain Langlois E et al. Guidelines of the French Society of Otorhinolaryngology (SFORL), short version. Extension assessment and principles of resection in cutaneous head and neck tumours. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131:375–383.	France	Resection in cutaneous HNC
Pfister DG, Spencer S, Brizel DM, Burtness B, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW et al. Head and Neck Cancers, Version 2.2014. J Natl Compr Canc Netw. 2014;12(10):1454–1487.	US	HNC treatment
Gregoire V, Leroy R, Heus P, Van de Wetering F, Hooft L, Scholten RJPM, Verleye L, Carp L, Clement P, Deron P, et al. Oral cavity cancer: Diagnosis, treatment and follow-up. In: Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). KCE Reports 227. 2013. https://kce.fgov.be/sites/default/files/atoms/files/KCE_227_oral_cavitycancer_Report_21.pdf . Accessed 1 Jul, 2020.	Belgium	Diagnosis, treatment and follow-up on oral cavity cancer
Mesia R, Pastor M, Grau JJ, del Barco E. SEOM clinical guidelines for the treatment of head	Spain	HNC treatment

CPG citation	Country (first author)	CPG topic
and neck cancer (HNC) 2013. Clin Transl Oncol. 2013;15:1018–1024.		
Pfister DG, Ang K-K, Brizel D, Burtness BA, Busse PM, Caudell JJ, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW et al. Head and Neck Cancers, Version 2.2013. J Natl Compr Canc Netw. 2013;11(8):917–923.	US	HNC treatment
Pfister DG, Ang K-K, Brizel D, Burtness BA, Busse PM, Cmelak AJ, Colevas AD, Dunphy F, Eisele DW, Gilbert J et al. Mucosal Melanoma of the Head and Neck. J Natl Compr Canc Netw. 2012;10:320–338.	US	Mucosal melanoma of the head and neck
Gregoire V, Lefebvre J-L, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl. 5):v184–v186.	Belgium	Diagnosis, treatment and follow-up on squamous cell carcinoma of the head and neck
Mesia Nin R, Pastor Borgonon M, Cruz Hernandez JJ, Isla Casado D. SEOM clinical guidelines for the treatment of head and neck cancer. Clin Transl Oncol. 2010;12:742–748.	Spain	HNC treatment

Table 3: Average Appraisal Scores and Average Overall Assessments of Each CPG

CPG	Metric	Appraiser 1	Appraiser 2	Average	Standard deviation
Nekhlyudov 2017 (Overall)	Appraisal Score	5.6	5.8	5.7	0.1
	Overall Assessment	6.0	5.0	5.5	0.5
Nekhlyudov 2017 (CAM Section)	Appraisal Score	4.0	4.0	4.0	0.0
	Overall Assessment	2.0	4.0	3.0	1.0
Choo 2016 (Overall)	Appraisal Score	6.0	6.3	6.2	0.2
	Overall Assessment	5.0	6.0	5.5	0.5
Choo 2016 (CAM Section)	Appraisal Score	4.3	4.0	4.2	0.1
	Overall Assessment	3.0	4.0	3.5	0.5
Cocks 2016 (Overall)	Appraisal Score	4.2	3.7	4.0	0.3
	Overall Assessment	5.0	3.0	4.0	1.0
Cocks 2016 (CAM Section)	Appraisal Score	3.3	2.9	3.1	0.2
	Overall Assessment	3.0	2.0	2.5	0.5
Talwar 2016 (Overall)	Appraisal Score	4.3	3.7	4.0	0.3
	Overall Assessment	5.0	4.0	4.5	0.5
Talwar 2016 (CAM Section)	Appraisal Score	3.7	3.3	3.5	0.2
	Overall Assessment	4.0	4.0	4.0	0.0

Table 4: Overall Recommendations for Use of Appraised CPGs

CPG	Overall CPG		CAM Section	
	Appraiser 1	Appraiser 2	Appraiser 1	Appraiser 2
Nekhlyudov 2017 [15]	Yes with Modifications	Yes with Modifications	Yes with Modifications	Yes with Modifications
Choo 2016 [16]	Yes with Modifications	Yes with Modifications	Yes with Modifications	Yes
Cocks 2016 [17]	Yes with Modifications	Yes with Modifications	No	No
Talwar 2016 [19]	Yes with Modifications	Yes with Modifications	Yes with Modifications	Yes with Modifications

Table 5: Scaled Domain Percentages for Appraisers of Each CPG

CPG		Domain score (%)					
		Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial Independence
Nekhlyudov 2017 [15]	Overall CPG	100.0	77.8	82.3	94.4	39.6	83.3
	CAM Section	100.0	38.9	42.7	75.0	2.1	83.3
Choo 2016 [16]	Overall CPG	100.0	86.1	80.2	88.9	83.3	79.2
	CAM Section	97.2	41.7	45.8	52.8	27.1	79.2
Cocks 2016 [17]	Overall CPG	91.7	58.3	33.3	83.3	35.4	4.2
	CAM Section	91.7	44.4	19.8	58.3	14.6	4.2
Talwar 2016 [19]	Overall CPG	83.3	52.8	37.5	86.1	47.9	4.2
	CAM Section	86.1	33.3	30.2	72.2	35.4	4.2