The Use of Dermoscopy in the Delineation of Basal Cell Carcinoma for Mohs Micrographic Surgery: a Systematic Review With Meta-Analysis

Noureddine Litaiem¹,², Faten Hayder¹,², Imene Benlagha¹,², Manel Karray¹,², Chadli Dziri²,³, Faten Zeglaoui¹,²

¹ Department of Dermatology, Charles Nicolle Hospital, Tunis, Tunisia
² University of Tunis El Manar, Faculté de Médecine de Tunis, Tunis, Tunisia; ³ Director of Honoris Medical Simulation Center, Tunisia

Key words: Mohs micrographic surgery, Slow Mohs, dermoscopy, dermatoscopy, basal cell carcinoma

Citation: Litaiem N, Hayder F, Benlagha I, Karray M, Dziri C, Zeglaoui F. The Use of Dermoscopy in the Delineation of Basal Cell Carcinoma for Mohs Micrographic Surgery: A Systematic Review with Meta-Analysis. Dermatol Pract Concept. 2022;12(4):e2022176. DOI: https://doi.org/10.5826/dpc.1204a176

Accepted: February 18, 2022; Published: October 2022

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Funding: None.

Competing interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding author: Noureddine Litaiem, Department of dermatology, Charles Nicolle Hospital, Tunis, Tunisia. E-mail: Noureddine.litaiem@gmail.com

ABSTRACT

Introduction: Several studies investigated the use of dermoscopy in the delineation of basal cell carcinoma (BCC) for Mohs micrographic surgery (MMS) with conflicting results.

Objectives: The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of the use of dermoscopy-guided MMS in the treatment of BCC.

Methods: We included all comparative studies. Cases of BCC treated using dermoscopy-guided MMS (or slow MMS) were compared to those treated with curettage-guided MMS or “standard” MMS.

Results: A total of 6 studies including 508 BCCs were reviewed. There was no statistically significant difference in the proportion of total margin clearance on the first MMS stage between BCCs removed using dermoscopy-guided MMS and those that had curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS.

Conclusions: Dermoscopy allows visualization of structures up to 1mm into the dermis. Therefore, it is rational to use it for lateral margin evaluation. Currently, there are two comparative studies showing the efficacy of dermoscopy for lateral margin evaluation during MMS. Future studies are required to develop an evidence-based recommendation regarding the utility of dermoscopy in MMS.
Introduction

Basal cell carcinoma (BCC) is the most prevalent skin cancer worldwide [1]. The overall incidence has been steadily rising in the last decade throughout the world due to a burgeoning aging population and increased surveillance and diagnosis [2].

The biological behavior of BCC depends on the tumor subtype [1,2]. Undiagnosed and untreated BCC could lead to extensive local destruction and increase both functional and cosmetic morbidity making the treatment and repair approach challenging for the physician.

The National Comprehensive Cancer Network (NCCN) has established guidelines of care for BCCs [3]. High-risk BCCs include recurrent BCC, tumors with ill-defined borders, located on high-risk mask area of the face, arising on sites of prior radiation therapy or harboring aggressive histological features [3]. There are multiple treatment options for BCC such as ablative laser, photodynamic therapy, curettage, cryosurgery, imiquimod, and sonic hedgehog pathway inhibitors [12,2]. However, surgical excision remains the gold standard for treatment of most BCCs [1]. Standard excision is performed with a predefined clinical margin in order to achieve low recurrence rates. Mohs micrographic surgery (MMS) is a specialized surgical technique that combines surgery with pathology. MMS uses horizontal frozen sections to obtain complete margin control resulting in minimal tissue removal with low recurrence rates [1]. MMS proved to be superior to standard excision for high-risk BCC [1]. Slow Mohs is a variant of MMS using formalin-fixed paraffin-embedded sections with similar outcome [4].

Dermoscopy, also known as dermatoscopy or epiluminescence microscopy, is a non-invasive imaging technique widely employed for the diagnosis of skin cancers. Some specific dermoscopic patterns are helpful in the diagnosis of BCC [5]. The use of dermoscopy in the demarcation of surgical margins is another scope of its application. For instance, the use of dermoscopy in MMS might help reduce the number of Mohs stages and achieve surgical margin control within the 1st Mohs stage [4,6-11].

Many studies investigated the effectiveness of dermatoscopy in tumor delineation for MMS but with varying outcomes [4,6-11]. While some suggested that dermatoscopy could help reduce the number of Mohs stages and therefore shorten operative time and cost [4,9,11], others argued against the usefulness of this approach [6,12]. The ambiguity of these findings is further hampered by the lack of randomized studies and systematic reviews.

Objectives

The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of the use of dermoscopy-guided MMS in the treatment of BCC.

Methods

Search Strategy

This systematic review with meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. We searched the PubMed and Scopus databases from inception up to January 26, 2022 to identify eligible studies. We aimed to identify all relevant studies published in English language. We used the following search algorithm: (“Basal cell carcinoma”) AND (“Mohs surgery” or “Slow Mohs” or “micrographic surgery” or “3-D histology” or “microscopically controlled surgery”) AND (“dermoscopy” or “dermatoscopy” or “epiluminescence microscopy”). The PubMed and Scopus search strategies are available as supplementary material.

Inclusion and Exclusion Criteria of Studies

Two review authors (NL and FH) independently screened titles and abstracts for eligible studies. Eligible articles were identified on the basis of the following inclusion criteria: (i) comparative studies having at least a group of BCCs treated with dermoscopy-guided MMS, (ii) studies that used a control group of BCCs treated with visual inspection and/or curettage-guided MMS, (iii) articles published in English language. For eligible studies, full articles were retrieved in full and analyzed by two independent authors (NL and FH). Any discrepancy between the two investigators was resolved by consensus.

PICO(S): Populations, Interventions, Comparison, Outcome Measures, Types of Studies

We included all comparative observational as well as randomized clinical trials (RCT). Participants with BCC regardless of the clinical and histological subtype of the tumor were eligible for inclusion.

Cases of BCC treated using dermoscopy-guided MMS (or slow MMS) were compared to those treated with curettage-guided MMS or “standard” MMS. The latter uses visual inspection alone to delineate the tumors. All types of dermoscopy techniques were eligible, regardless of the polarization mode (polarized vs. nonpolarized mode) and the device type (hand-held dermatoscopy or video dermatoscopy).

The main outcome measure was the proportion of total margin clearance on the first MMS stage. The secondary outcome measures included the: (i) number of Mohs stages required to achieve complete margin control, (ii) the lateral margin involvement rate, and (iii) the recurrence rate.

If one or more outcome measures were missing, we contacted the corresponding author at least twice (with at least one-week interval) to ask whether full data were available. If the contact was unsuccessful, the corresponding article was excluded from the analysis.
Assessment of the risk of bias
Two review authors (NL and FH) independently assessed the quality of consistency and the risk of bias in the eligible studies. Any disagreement was resolved by discussion or by consensus with a third author (CD). MINORS score was used for observational studies [14]. RCT were evaluated using the Jadad score [15].

Data Synthesis and Statistical Analysis
Results were reported as Odds ratio (OR) with 95% confidence intervals (CIs) for dichotomous data (proportion of total margin clearance on the first MMS stage, lateral margin involvement, and recurrence rates) and standardized mean difference with standard error of the mean for continuous data (number of Mohs stages). A random-effects model was used. Forest plots summarized the data. Funnel plot was used to investigate the existence of publication bias. Strategies for addressing heterogeneity included performing a random-effects meta-analysis and subgroup analyses. We performed all calculations using Comprehensive meta-analysis 3.0 package.

We investigated heterogeneity using Cochran Q test. Evaluation of the percentage of variation between the sample estimates was performed using the Higgins $I^2$ statistic.

Results

Results of the Search
The literature search identified 289 articles (Figure 1). After removing duplicates, 69 articles were screened for eligibility. Fifty-five records were excluded, including not relevant articles ($N = 30$), papers not published in English ($N = 3$), editorials and commentary ($N = 11$), review articles ($N = 10$) and book chapters ($N = 2$). Fourteen full-text articles were assessed for eligibility. Among these, 4 were excluded (case reports and noncomparative studies) [16-19]. Three research letters were excluded [11,20,21]. Among these research

![Figure 1. Flow diagram.](image-url)
letters, two compared dermoscopy to naked eye examination in BCC margin evaluation but the number of Mohs stages in each study group expressed in mean with standard deviation was not available [11,20]; and one article included only BCC evaluated using dermoscopy prior to MMS [21].

A randomized open-label study comparing visual inspection, curettage, and dermoscopy in tumor delineation for MMS was excluded because no outcome measure was available for each study group [12]. Contact with the corresponding authors of this study was unsuccessful. Six articles were ultimately included in the present systematic review. Of these, 2 studies were from Asia-Pacific region, 1 from North America, 1 from South America, 1 from Europe, and 1 from Africa (Table 1) [4,6-10].

**Description of Included Studies**

Of the 6 included studies, 2 were RCTs [6,7], and four were observational studies [4,8-10]. There was no randomized controlled study available for the present systematic review. All included studies were conducted in university-setting centers [4,6-10]. These studies had no funding support and corresponding authors declared no conflicts of interest [4,6-10].

The number of BCCs evaluated ranged from 40 to 197 BCCs per study. The total number of evaluated BCCs was 508. Suzuki et al included both BCC (N = 40) and squamous cell carcinomas (N = 6). The latter were excluded from the analysis. Three studies specified BCC subtypes [6,7,9]. Asilian and Momeni included only nodular BCC [6], and Gurggen and Gatti only infiltrative BCC [7]. Dika et al included various BCC subtypes including nodular (N = 40) and morphoform BCCs (N = 40) [9].

Recurrent BCCs were excluded in three studies [4,6,7]. One study included only recurrent BCC following ablative laser treatment [10]. Two studies enrolled both primary and recurrent BCC (Table 1) [8,9].

Four studies compared 2 interventions for MMS: tumor delineation using naked eye examination versus dermoscopy-guided margin assessment [4,7,8,10]. One of the studies compared dermoscopy-guided MMS to curettage-guided MMS [9]. Asilian and Momeni compared 3 groups: tumor demarcation using naked eye examination (N = 20), dermoscopy (N = 20) and curettage (N = 20) [6].

For the primary outcome “total margin clearance on the first MMS stage”, we assumed that BCCs that underwent more than one Mohs stage showed at least one positive margin. Thereby, the number of BCCs showing total margin clearance on the first MMS stage was extracted from 5 articles [4,7-10].

The secondary outcomes included the mean number of Mohs stages, the recurrence rate, and the number of positive lateral margins after the first Mohs stage.

The mean number of Mohs stages in each study group was specified in 5 articles [4,6-9]. However, related standard deviations were only available in 3 articles [4,6,7]. Contact with the corresponding authors of these studies was unsuccessful. Therefore, we did not have the required data to carry out the up-mentioned analysis for these articles [4,6,7].

Only two studies reported the number of positive lateral margins after the first Mohs stage [4,10].

Relapse rates were described in 2 articles [4,9], ranging between no relapse and 4%, after a follow-up period of 10 ± 5 and more than 62.5 months respectively.

**Assessment of Risk of Bias in Included Studies**

For RCT [6,7], the Jadad scale was 1 and 2. Overall, the methodological quality was poor. There was no disagreement between the review authors (NL and FH) about the studies quality.

For non-randomized studies [4,8-10], the MINORS index ranged between 14 and 16.

**Effects of Interventions**

When comparing dermoscopy-guided vs. standard MMS for BCC treatment, there was no statistically significant difference in the proportion of total margin clearance on the first MMS stage (OR 0.86, 95% CI 0.41 to 1.15; five studies [4,7-10]) (Figure 2).

There was no statistically significant difference in the number of Mohs stages when comparing dermoscopy-guided and standard MMS (The standardized mean difference -0.17, 95% CI -0.51 to 0.17; three studies [4,6,7]) (Figure 3). For this outcome measure, we found heterogeneity (Tau2 = 0.220 et I2 = 70.334%). Subgroup analysis was performed based on the technique used for Mohs surgery (frozen sections versus formalin-fixed paraffin-embedded sections). After subgroup analysis, including studies using MMS [6,7], there was no heterogeneity (Tau2 = 0.000), the pooled standard difference in means showed no statistically significant difference. Only one study reported the number of Mohs stages in patients treated using Slow Mohs [4]. Since iterative Mohs sessions rely on histopathological examination of excised tissue, it is possible that the type of tissue processing technique (frozen sections in MMS vs formalin-fixed paraffin-embedded sections in slow Mohs) is responsible for heterogeneity regarding the outcome measure (number of Mohs stages).

A significantly lower proportion of positive lateral margins was obtained with dermoscopy-guided MMS compared with standard MMS based on visual inspection (OR 0.16, 95% CI 0.06 to 0.83; 2 studies [4,10]) (Figure 4).

With regards to recurrence rates, available data was insufficient for meta-analysis. Two studies reported the number of recurrences after MMS [4-9]. One of these...
| Author                        | Year | Country   | Study objective                                                   | Study design   | Coverage period | Intervention groups                                                                                     | BCC subtypes in each group | Follow-up (months) | Cases included in the meta-analysis |
|------------------------------|------|-----------|------------------------------------------------------------------|----------------|----------------|-------------------------------------------------------------------------------------------------------|----------------------------|-------------------|-------------------------------|
| Asilian and Momeni [6]       | 2012 | Iran      | To compare three ways (naked eye examination, dermoscopy, and curettage) for determining tumor extension before initiation of MMS, and to compare these methods to each other. | RCT            | 2011-2012      | 3 groups: tumor demarcation using naked eye examination (N = 20), dermoscopy (N = 20), and curettage (N = 20) | nodular BCC in all included cases | 40                | not included in the study       |
| Gurgen and Gatti [7]         | 2012 | United States | To compare the final number of MMS stages performed using dermoscopy and visual inspection of infiltrative basal cell carcinoma with and without dermoscopy. | RCT            | ND             | 2 groups: dermoscopy group (N = 20) and visual inspection group (N = 20) | infiltrative BCC in all cases | ND                | not included in the study       |
| Suzuki et al [8]             | 2014 | Brazil    | To assess the impact of dermoscopy on the demarcation of the surgical margins for MMS and ascertain whether the use of this method can shorten operative time. | observational study | 2009-2011 | 2 groups: Group1: MMs surgery (N = 21) and Group 2: MMs surgery with dermoscopy-guided margins (N = 23) | ND                         | 44                | Group 1: 3/21; Group 2: 4/23   |
Table 1. Summary of included studies. (continued)

| Author          | Year | Country | Study objective                                                                 | Study design          | Coverage period | Intervention groups                                                                 | BCC subtypes in each group                                                                                                                                                                                                 | Recurrent BCC before Mohs surgery | Cases included in the meta-analysis | Follow-up (months) |
|-----------------|------|---------|----------------------------------------------------------------------------------|-----------------------|-----------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|-------------------------------|------------------|
| Dika et al      | 2017 | Italy   | to evaluate the role of videodermoscopy and curettage in MS for a better margin evaluation intraoperatively | observational study   | 2005-2010       | 2 groups:                                                                            | Group 1: - nodular BCCs (N = 21)  
Group 2: - pigmented BCCs (N = 28)  
Group 3: - morpheiform BCCs (N = 20) | All cases were recurrent BCC (previously treated by ablative laser). Recurrent cases after radiotherapy or surgical resection were excluded. | 197              | Group 1 (82.6)  
Group 2 (62.5)  |
| Shin et al      | 2020 | Korea   | To evaluate the usefulness of dermoscopy in determining MMS surgical margins of BCCs with a history of ablative laser treatment. | observational study   | 2009-2016       | 2 groups:                                                                            | ND                                                                             | ND                           | 133              | ND                           |
| Author | Year | Country | Study objective | Study design | Coverage period | Intervention groups | BCC subtypes in each group | Recurrent BCC before Mohs surgery | Cases included in the meta-analysis | Follow-up (months) |
|--------|------|---------|-----------------|--------------|----------------|---------------------|---------------------------|-------------------------------|---------------------------------|-----------------|
| Litaiem et al [4] | 2020 | Tunisia | To evaluate the use of dermoscopy in the demarcation of surgical margins in slow Mohs surgery. | observational study | 2016-2019 | 2 groups: G1: tumor demarcation using naked eye examination (N = 28) G2: tumor demarcation using naked eye examination + dermoscopy (N = 26) | ND | not included in the study | 54 | 10 ± 5 |

BCC = basal cell carcinoma; ND = not described; RCT = randomized clinical trial.
studies reported a recurrence rate of 3% in BCCs treated with dermoscopy-guided MMS and of 5.2% in those treated with curettage-guided MMS (P = 0.48; Fisher exact test) after a follow-up period of 82.6 and 62.5 months respectively [9]. In the second study, both study groups showed no recurrence after a mean follow-up period of 10 ± 5 months [4].

Conclusions

In the present study, we aimed to assess the effectiveness of dermoscopy as an ancillary tool for MMS. Six studies were included: 2 RCTs [6,7], and 4 observational studies [4,8-10]. The total number of evaluated BCCs was 508. Three studies specified the subtypes of evaluated BCCs [6,7,9]. Three studies excluded recurrent BCC [4,6,7], while one study included only recurrent BCC following ablative laser [10]. Of the included studies, pooling of the data was feasible for 3 evaluated outcomes. There was no statistically significant difference in the proportion of total margin clearance on the first MMS stage between BCCs removed using dermoscopy-guided MMS and those that had curettage or visual inspection. However, lateral margin involvement was significantly lower in BCCs that had dermoscopy-guided MMS.

To the best of our knowledge, no systematic review addressed the question of whether dermoscopy is useful for delineating BCC margins for MMS. Que published a comprehensive narrative review on noninvasive imaging technologies used for the delineation of BCC in the setting of
Figure 3. Comparison of the number of Mohs stages using dermoscopy-guided vs. standard or curettage MMS for BCC treatment.

Figure 4. Comparison of the proportion of positive lateral margins after the first Mohs stage using dermoscopy-guided vs. standard or curettage guided MMS for BCC treatment.
MMS [22]. Three technologies were discussed: dermoscopy, confocal microscopy, and optical coherence tomography. Only the number of Mohs stages was evaluated as an outcome measure in relation to dermoscopy. Que stated that dermoscopy did not prove to decrease the number of Mohs stages. In our systematic review, there was no statistically significant difference in the number of Mohs stages between the use of dermoscopy or visual inspection for MMS (the standardized mean difference -0.17, 95% CI -0.51 to 0.17; three studies [4,6,7]). A hypothesis to explain this finding is that dermoscopy utility is limited to the first Mohs stage. Subsequent stages would only rely on the surgeon’s skills and experience.

In the present systematic review, there was no significant association between the use of dermoscopy and the proportion of total margin clearance on the first MMS stage. Surgical margin assessment includes both deep and lateral margin evaluation. A dermoscope is a magnifying instrument that enables visualization of pigmented structures and vessels up to 1mm into the dermis and therefore would not allow for deep margin evaluation [5]. Hence, it is rational to use it for lateral margin evaluation [4,10].

There are several potential implications for both practice and research. Relapsing BCCs and BCCs bearing aggressive histopathological features may exhibit a subclinical extension of their lateral margins [23]. This could result in recurrences and incomplete surgical excision [23]. Further studies assessing lateral margin involvement are needed. In addition, future research is warranted to investigate the utility of dermoscopy for tumor delineation in high-risk BCC.

Combining two imaging techniques is beyond the scope of the present systematic review. Recently, Lupu et al evaluated whether BCC lateral excision margins could be precisely evaluated preoperatively through the use of dermoscopy and reflectance confocal microscopy [23]. In this study, 18 patients (20 BCCs, mostly nodular: 12/20) were included. The authors concluded that dermoscopy served as an accurate guide during reflectance confocal microscopy [23]. The global accuracy of the procedure was 93.1% (95% CI 0.77–0.99) [23].

The present systematic review sought to summarize the existing data on the possible use of dermoscopy for tumor delineation in MMS. However, certain limitations apply to the results depicted herein. First, our sample size was limited by the scarcity of research on this subject in the literature. Only two included studies evaluated the use of dermoscopy for lateral margin assessment. Therefore, these results should be interpreted with caution. Second, some studies had missing data on outcome measures and hence were excluded from the data analysis. Third, the histopathological subtype of BCC, which can act as a confounding factor, was not indicated in all included studies. This may hinder the interpretation of findings and undermine their accuracy. Finally, both dermoscopy and MMS are operator-dependent procedures [4]. Thus, controlled, consistent and reproducible results are not readily attainable.

Despite these limitations, this systematic review is a comprehensive summary on the reported use of dermoscopy for BCC delineation in MMS to date. Overall, our data suggest that dermoscopy could improve lateral margin assessment within the first Mohs stage. Future randomized clinical trials are required to develop an evidence-based recommendation regarding the utility of dermoscopy in MMS.

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Supplementary File 1

Pubmed search strategy

#1. “Basal cell carcinoma” AND “Mohs surgery” AND “dermoscopy”
#2. “Basal cell carcinoma” AND “Mohs surgery” AND “dermatoscopy”
#3. “Basal cell carcinoma” AND “Mohs surgery” AND “epiluminescence microscopy”
#4. “Basal cell carcinoma” AND “micrographic surgery” AND “dermoscopy”
#5. “Basal cell carcinoma” AND “micrographic surgery” AND “dermatoscopy”
#6. “Basal cell carcinoma” AND “micrographic surgery” AND “epiluminescence microscopy”
#7. “Basal cell carcinoma” AND “3-D histology” AND “dermoscopy”
#8. “Basal cell carcinoma” AND “3-D histology” AND “dermatoscopy”
#9. “Basal cell carcinoma” AND “3-D histology” AND “epiluminescence microscopy”
#10. “Basal cell carcinoma” AND “microscopically controlled surgery” AND “dermoscopy”
#11. “Basal cell carcinoma” AND “microscopically controlled surgery” AND “dermatoscopy”
#12. “Basal cell carcinoma” AND “microscopically controlled surgery” AND “epiluminescence microscopy”

Scopus search strategy

#1. TITLE-ABS-KEY (“basal cell carcinoma” AND “mohs surgery” AND “dermoscopy”)
#2. TITLE-ABS-KEY (“Basal cell carcinoma” AND “Mohs surgery” AND “dermatoscopy”)
#3. TITLE-ABS-KEY (“Basal cell carcinoma” AND “Mohs surgery” AND “epiluminescence microscopy”)
#4. TITLE-ABS-KEY (“Basal cell carcinoma” AND “micrographic surgery” AND “dermoscopy”)
#5. TITLE-ABS-KEY (“Basal cell carcinoma” AND “micrographic surgery” AND “dermatoscopy”)
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#10. TITLE-ABS-KEY (“Basal cell carcinoma” AND “microscopically controlled surgery” AND “dermoscopy”)
#11. TITLE-ABS-KEY (“Basal cell carcinoma” AND “microscopically controlled surgery” AND “dermatoscopy”)
#12. TITLE-ABS-KEY (“Basal cell carcinoma” AND “microscopically controlled surgery” AND “epiluminescence microscopy”)

Review | Dermatol Pract Concept. 2022;12(4):e2022176
## Supplementary File 2

| Section and Topic | Item # | Checklist item | item reported in line # |
|-------------------|--------|----------------|-------------------------|
| TITLE             | 1      | Identify the report as a systematic review. | 3                        |
| ABSTRACT          | 2      | See the PRISMA 2020 for Abstracts checklist. | 5-23                     |
| INTRODUCTION      | 3      | Describe the rationale for the review in the context of existing knowledge. | 49-57                   |
|                   | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 58-59                   |
| METHODS           | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 72-87                   |
| Eligibility criteria | 6      | Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 61-65                   |
| Information sources | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 65-69                   |
| Search strategy   | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 71-72                   |
| Selection process | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 71-78                   |
| Data collection process | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 89-95                   |
| Data items        | 10b    | List and define all other variables for which data were sought (eg participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 89-95                   |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 96-101                  |
| Effect measures   | 12     | Specify for each outcome the effect measure(s) (eg risk ratio, mean difference) used in the synthesis or presentation of results. | 103-106                 |

*Table 1 continues*
| Section and Topic       | Item # | Checklist item                                                                                                                                                                                                 | item reported in line # |
|------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Synthesis methods      | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (eg tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).                                      | 152-165                |
|                        | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.                                                                 | 102-106                |
|                        | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                           | 103-106 Table 1        |
|                        | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.                                      | 106-110                |
|                        | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (eg subgroup analysis, meta-regression).                                                                                          | 107-109                |
|                        | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                     | -                      |
| Reporting bias assessment | 14    | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                          | 95-99                  |
| Certainty assessment   | 15    | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                          | 103-106                |
| RESULTS                |        |                                                                                                                                                                                                             |                         |
| Study selection        | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.                                    | 115-130                |
|                        | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.                                                                                       | 119-127                |
| Study characteristics   | 17    | Cite each included study and present its characteristics.                                                                                                                                                      | 127-130                |
| Risk of bias in studies | 18    | Present assessments of risk of bias for each included study.                                                                                                                                                  | 166-170                |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure 2-4             |
| Results of syntheses   | 20a    | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.                                                                                                          | Figure 2-4 (funnel plot) |
|                        | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Figure 2-4             |
|                        | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                                  | 177-186                |
|                        | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                    | -                      |
| Reporting biases       | 21    | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.                                                                                         | 166-170                |
| Certainty of evidence  | 22    | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.                                                                                                            | 171-195 figures 2-4    |
| DISCUSSION             | 23a    | Provide a general interpretation of the results in the context of other evidence.                                                                                                                              | 197-207                |
|                        | 23b    | Discuss any limitations of the evidence included in the review.                                                                                                                                              | 243-253                |
|                        | 23c    | Discuss any limitations of the review processes used.                                                                                                                                                       | 243-253                |
|                        | 23d    | Discuss implications of the results for practice, policy, and future research.                                                                                                                              | 228-233                |
| Section and Topic | Item # | Checklist item | item reported in line # |
|-------------------|--------|----------------|-------------------------|
| OTHER INFORMATION |        |                |                         |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | not registered |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | the review protocol was not published. |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | not registered |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 261-262 |
| Competing interests | 26 | Declare any competing interests of review authors. | 264-265 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 266-268 |

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. DOI: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924. For more information, visit: http://www.prisma-statement.org/