

## **Cost effectiveness of Mohs micrographic surgery for non-melanoma skin cancer: a systematic review protocol**

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## Review title

Cost effectiveness of Mohs micrographic surgery for non-melanoma skin cancer: a systematic review protocol

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## Background

### ***Description of the condition: definition and epidemiology***

Non-melanoma skin cancers (NMSCs) represent a cluster of neoplasms that together are not only the most common type of skin cancers, but also the most common cancer in general worldwide.<sup>1-4</sup>

Although there are a number of diseases included in this general class of cutaneous neoplasms, NMSCs consist primarily of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).<sup>5</sup> BCC is the most common type of NMSC, accounting for up to 80% of cases, with an incidence ranging from as low as 47.4 in women from Scotland to 1541.0 in men from Australia per 100,000 individuals.<sup>5</sup> SCC is the second most common type of NMSC: its incidence per 100,000 individuals ranges from 5.3 in women from Germany to 772.0 in men from Australia.<sup>5</sup> The most important risk factor for NMSC is exposure to solar radiation, which can be influenced by various other related variables such as having lighter skin pigmentation, maintaining outdoor occupations and lack of sun protection behaviors.<sup>6-8</sup> Sun exposed skin surfaces, such as the head and neck, are the most common site of appearance for NMSC.<sup>1,9</sup>

NMSC can be deadly, particularly SCC. The early precursors of SCC, known as actinic keratosis on glabrous skin<sup>8,10-12</sup> and solar cheilosis on the lips<sup>6,13</sup> are generally benign. However, they can be potentially fatal if they develop into SCC and the mortality risk is even higher for SCC of the lips.<sup>6</sup> BCC, on the other hand, is unlikely to metastasize and thus has a lower mortality rate than SCC. NMSC does not cause substantial social stigma in its early stages because it generally takes a long time to develop. As a result, patients with BCC, for example, often delay seeing a physician for a longer period of time than those with more visible skin diseases such as psoriasis.<sup>14</sup> However, in its advanced stages, BCC can cause severe disfigurement at the site where it is detected<sup>15</sup> and can therefore have a substantial impact on patients' quality of life. This is particularly true because, like the majority of NMSCs, BCC tends to occur on sun-exposed surfaces, particularly the face, scalp, neck and arms, which are areas that are clearly visible and potentially influential in terms of social stigma and the patient's self-esteem.

### ***Description of the intervention: clinical effectiveness of surgical versus medical approaches***

There are many different therapeutic modalities for NMSC, ranging from medical treatments with topical 5-fluorouracil (5-FU) and imiquimod immunotherapy, to surgical treatments such as cryosurgery, radiotherapy, electrodesiccation and curettage (ED&C), excisional surgery and Mohs

micrographic surgery (MMS).<sup>2,5,9,16-18</sup> Once the diagnosis is established clinically and confirmed histologically, treatment selection depends primarily on the type of cutaneous neoplasm (i.e. BCC vs. SCC vs. other type of NMSC), the site of the lesion (i.e. cosmetically or anatomically sensitive or not), and the disease stage and subtype based on the histological analysis. Additional considerations, however, include comorbidities (such as immunosuppression), local expertise, availability of treatment methods and particularly, the cost of the treatment.<sup>5,19</sup> While an extensive review of these treatments and their mechanisms of action is not warranted for the purposes of this systematic review, general descriptions and recommendations on the use of these therapies are provided below.

*MMS* is a surgical technique that has been accepted in practice since 1989.<sup>20</sup> It consists of the surgical removal of a skin tumor with specified margins, followed by tissue section and microscopic analysis in the office, with repeat excision as necessary to ensure complete clearance of the tumor from the anatomic site.<sup>19,21</sup> It is generally recommended for high-risk tumors of the head and neck.<sup>9,22-24</sup> *Excisional surgery* is the most common treatment for NMSC and is used for lower risk tumors.<sup>17,25</sup> It is also a preferred method because like MMS, it yields tissues that can be analyzed histologically.<sup>17,21</sup> *ED&C* consists first of the destruction of the tissue (i.e. electrodesiccation), followed by scraping away of the necrotic tissue (i.e. curettage): this procedure is used for superficial NMSC lesions.<sup>17,25,26</sup> *Radiotherapy* is useful for NMSC in patients who are unable to tolerate surgery.<sup>17,25</sup> *Cryosurgery* involves the topical application of liquid nitrogen to freeze and destroy tumor cells. It may be used for tumors with well-defined borders and in debilitated patients.<sup>17,25</sup> The latter three ablative procedures do not allow for histological analysis, as the tissue removed is destroyed in the process.

The most commonly used medical treatment for superficial non-invasive NMSC is *topical 5-FU*.<sup>17,25</sup> It induces tumor cell death, which manifests clinically as a severe inflammatory reaction at the site of application. *Imiquimod immunotherapy*, also applied topically, results in a less severe inflammatory reaction than 5-FU and is effective for superficial and nodular BCC, as well as SCC in situ.<sup>17,25</sup> Other chemotherapeutic treatments include *photodynamic therapy*<sup>27</sup> and *intralesional interferons*,<sup>17,25</sup> however these are only used under limited circumstances, as the former has a high recurrence rate, even with clinically apparent resolution of the lesions, while the latter has a low cure rate and requires frequent and multiple injections, which can deter patient adherence.<sup>25</sup> Systemic *retinoids* are thought to be chemo-preventive by reducing the risk of developing NMSC.<sup>25</sup>

Four systematic reviews were found, three of which are published in the Cochrane Library, on the clinical effectiveness of these various treatments for SCC and BCC.<sup>28-31</sup> One Cochrane systematic review on the effectiveness of treatments for localized SCC (an indication for using MMS if present in a cosmetically or anatomically sensitive location), found no significant difference between excisional surgery and radiation combination therapy with or without adjuvant 13-cis-retinoic acid and interferon alpha.<sup>29</sup> This conclusion was based on only one randomized controlled trial (RCT) that did not evaluate the use of MMS and non-RCT studies comparing the use of various treatments for SCC were excluded. Another Cochrane systematic review on the effectiveness of treatments for BCC found that MMS and excisional surgery are equivalent with regards to recurrence.<sup>28</sup> This conclusion also has two similar limitations: first, it is based on the results of only a single high quality RCT and second, evidence from well conducted, comparative observational studies was not considered even though it is available.<sup>32</sup> A systematic review that used prospective comparative observational studies in addition to experimental studies found that MMS has a lower recurrence rate than all other treatment modalities,<sup>31</sup> which conflicts with the findings of the Cochrane systematic review that used RCTs only. Although observational studies can be used to detect the clinical effectiveness of interventions in the absence of RCTs, in this systematic review, the fact that studies were not critically appraised for risk of bias may have compromised the validity of the synthesized results. Finally, a Cochrane systematic review conducted on the clinical effectiveness of MMS as compared specifically to excisional surgery,<sup>30</sup> limited its outcomes to those relevant for periorbital BCC only (a subtype of NMSC in a high-risk anatomic location) and to a search for RCTs only. No experimental studies were found, resulting in an empty review that called for further primary research on this pressing clinical question.<sup>30</sup>

In summary, all of these reviews found either that there are no RCTs on the clinical effectiveness of MMS, or that there are only a few high quality RCTs supporting the use of some of the surgical and/or medical treatments for NMSC. Thus, current practice guidelines informing the treatment of NMSC are primarily based on lower quality evidence than would otherwise be desired, such as observational studies and expert consensus.<sup>33-35</sup> In this context, where the best available evidence is unfortunately not the highest quality evidence, it becomes even more imperative to

understand which treatments have been found to have the highest cost effectiveness, cost utility and cost benefit from the patient's point-of-view, as well as from the provider, healthcare system and societal perspectives, taking into consideration the different contexts of care.

***How the intervention might work: economic implications of NMSC and its treatment***

Cost considerations have been at the forefront of treatment decision-making for NMSC for many years<sup>17</sup> and there has been a particularly significant debate with regards to MMS.<sup>36</sup> It has been argued that the number of practice-related factors that must be put in place in order to facilitate the use of MMS, such as the need to have trained Mohs surgeons available and to set up the support services required to allow the conduct of MMS, including a histopathology lab or referral service, has substantial implications for the cost effectiveness of MMS,<sup>5</sup> particularly from a healthcare system perspective. The economic impact of skin cancer management, from a societal or healthcare system standpoint, has been evaluated in many countries, with some data available specifically for NMSC. In the United States, the cost of treating NMSC in the Medicare population alone amounts between anywhere from \$426 to \$562 million/per year,<sup>37,38</sup> with the per episode cost of care being \$492, \$1043 and \$5537 when performed in a physician's office, other outpatient settings, and inpatient setting, respectively.<sup>37</sup> In the United Kingdom, the treatment of NMSC reached more than £100 million.<sup>39</sup> In Germany, up to €130 million were spent on caring for patients with NMSC in the hospital setting alone.<sup>40</sup>

From a cost utility (CUA) standpoint, in which costs are compared to the change in patients' quality of life (QOL),<sup>41</sup> the evidence for MMS and NMSC has yet to be synthesized in the published literature. In one study, MMS has similar QOL results when compared to traditional excisional surgery for NMSC and better QOL outcomes than ED&C.<sup>42</sup> The study used the Skindex scale, a validated QOL tool that measures the domains of symptoms, emotions and function. Another study examined the QOL of patients with NMSC, using the Dermatology Life Quality Index (DLQI) and found that NMSC had no significant QOL impact both before and after treatment. Yet neither of these studies had any cost considerations, which would have provided a relatively more realistic measure of the implications of treating NMSC for patients and the healthcare system. Clearly, there is a need for a systematic review of the existing evidence on the cost utility of MMS for NMSC.

Cost minimization (CMA) studies aim to compare the cost of clinically equivalent treatments.<sup>41</sup> From a cost perspective alone, MMS is often thought to be more expensive than other treatments for NMSC, although certain types of surgical treatments can rival or surpass it in this regard.<sup>17,43</sup> However, recently published systematic reviews have already shown that there is insufficient high quality research-based evidence on MMS, surgical excision and other treatments for NMSC to allow the formation of a well-founded judgment on their comparative clinical effectiveness.<sup>28-31</sup> Even expert consensus papers and guidelines suggest differential effectiveness of each treatment for the different types and grades of NMSC.<sup>33-35</sup> Thus, a comparison of only the cost of MMS to that of other treatments for NMSC may not provide a true research-based depiction of the economic effectiveness of MMS, from either the patient, healthcare system or societal perspective. However, CMA studies on MMS may still be valuable for healthcare decision-making purposes. This is because CMA studies base their assumptions of the equivalency in clinical outcomes for MMS compared to other treatment methods on established guidelines<sup>44-47</sup> and this makes the results of these CMA studies relevant for practicing clinicians. For this reason, CMA studies will also be pursued and included in this review.

Studies on cost effectiveness (CEA) and cost benefit (CBA) attempt to address this concern, by taking into account the relative cost and clinical effectiveness, presenting their results as and basing their recommendations on the incremental cost effectiveness ratio and cost benefit ratio, respectively.<sup>41</sup> There are many studies on the cost effectiveness of MMS. For example, one study has suggested that MMS may be less cost effective than excisional surgery for primary and recurrent BCC, yet clearly points out that its follow-up period may have been too short to detect the economic effectiveness of MMS for recurrent BCC.<sup>48</sup> An RCT with 5-year follow-up also reports that MMS is less cost effective than excisional surgery for both primary and recurrent BCC.<sup>49</sup> However, this study only considered treatment costs, taking on a healthcare system perspective in calculating costs. The study also mentions that post-operative complications such as necrosis of grafts, wound infection and bleeding, were dealt with similarly between the intervention and control group, but it did not report which group fared worse on those outcomes. Thus, by excluding the costs of these complications and other important factors that are more likely to occur with excisional surgery than with MMS, such as the destruction of more normal tissue and poorer cosmetic results,<sup>17,19,32</sup> the study may have

underestimated the cost effectiveness of MMS from a patient or societal standpoint. A very large multicenter prospective cohort study of MMS had very low rates of minor or serious adverse events, further strengthening this point.<sup>50</sup> Still, another study reports that MMS is actually more cost effective than excisional surgery.<sup>51</sup> In essence, given that studies differ in their findings, the need to conduct a systematic review of the evidence on the cost effectiveness of MMS for NMSC is well supported.

***Why it is important to do this review: current state of the health economic evidence on the use of MMS for NMSC***

It is clear that the cost of treating NMSC with MMS can be a substantial burden to society, healthcare systems and patients, particularly if the disease has reached advanced stages. In order to avoid these costs, there is a need to demonstrate which treatments for NMSC are most cost effective, which would allow healthcare and policy decisions to be made based on the best available evidence, taking into consideration both cost and clinical outcomes simultaneously. This need is even more pressing given that the incidence of NMSC is increasing worldwide.<sup>5</sup> A comprehensive search of the Cochrane Library, the Joanna Briggs Institute Library of Systematic Reviews and Implementation Reports, the PROSPERO database and Google Scholar yielded one systematic review of health economic evaluation studies for NMSC and actinic keratosis.<sup>52</sup> However, this study was performed close to a decade ago, during which time many new economic evaluation studies on this topic have been conducted and published, including higher quality designs such as RCTs. It also did not offer any method for the synthesis and integration of the data from the different studies found, which the proposed systematic review intends to do. Furthermore, that systematic review did not explicitly seek to determine the cost effectiveness of MMS as compared to all other treatments for NMSC, which is a more focused research question with pressing and current practice implications. Thus, it was concluded that no existing systematic review reports or protocols address the specific proposed research question. Therefore, this systematic review seeks to evaluate the published and unpublished literature to synthesize the evidence on the cost effectiveness of MMS for NMSC.

## **Review question/objective**

The overall research question for this systematic review is: what is the cost effectiveness of Mohs micrographic surgery for non-melanoma skin cancer in different contexts?

More specifically, the objectives are to:

- Identify, appraise and synthesize the evidence on the cost effectiveness, cost benefit, cost minimization and cost utility of MMS, compared to other surgical/ablative interventions such as excisional surgery and radiation therapy, as well as non-surgical/chemotherapeutic interventions such as topical 5-fluorouracil and imiquimod immunotherapy, for NMSC clinical care outcomes, covering the patient, provider, healthcare system and societal perspectives;
- Provide a comprehensive overview of existing knowledge and knowledge gaps on the relative economic and clinical effectiveness of this procedure for patients with NMSC in different contexts globally.

## **Inclusion criteria**

### **Types of participants**

This review will consider studies that include participants with an established diagnosis of NMSC. For the purposes of this review, an established diagnosis of NMSC will consist of either SCC or BCC, confirmed histologically, clinically or both, by a healthcare provider trained to do so.

### **Types of intervention(s) and comparator(s)**

This review will consider studies that evaluate MMS as a treatment for NMSC. An inclusive approach will be adopted with respect to comparators. The review will consider for inclusion both full and partial economic evaluations that have estimated the cost effectiveness of MMS as a treatment for NMSC compared to any known treatment comparator.

### **Types of outcomes**

This review will consider studies that have measured any clinical care outcomes related to NMSC, including but not limited to mortality, QOL, quality-adjusted life years (QALY), incidence and recurrence of NMSC lesions and frequency of adverse events. However, to be considered for inclusion, studies must also provide an economic evaluation of the relative costs of using MMS as a therapeutic modality when compared to other known treatment modalities.



### **Types of studies**

This review will consider CEA, CBA, CMA and CUA studies. Studies must include MMS as one intervention group and at least one other control or comparator group must be present. All experimental designs (i.e. randomized controlled trials, clinical controlled trials and quasi-experimental studies), observational designs (i.e. longitudinal prospective cohort studies and retrospective cohort studies such as case-control studies) as well as epidemiological designs (i.e. cross-sectional studies) with control or comparator groups will thus be included. The economic evaluation method used in the studies, whether it is model based or not, will not be a consideration for inclusion.

### **Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken, followed by analysis of the text words contained in the title and abstract and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles will be searched for additional studies. Studies published in all languages will be considered for inclusion in this review and efforts will be made to obtain English language translations of non-English language manuscripts. Although the American College of Mohs Micrographic Surgery and Cutaneous Oncology did not fully endorse MMS until 1985 (when it changed its name to reflect the widespread acceptance of the procedure), MMS was well known in the clinician community as early as 1969.<sup>20</sup> Thus, studies from 1969 to the present will be considered for inclusion in this review, as this is the earliest recorded date of the procedure being introduced in practice.

The databases to be searched include:

MEDLINE (Medical Literature Analysis and Retrieval System Online)  
CINAHL (Cumulative Index to Nursing and Allied Health Literature)  
EMBASE (Excerpta Medica Database)  
CENTRAL (Cochrane Central Register of Controlled Trials)  
HEED (Health Economic Evaluation Database)  
NHS EED (National Health Service Economic Evaluation Database)  
EURONHEED (European Network of Health Economic Evaluation Database)  
CEA (Cost Effectiveness Analysis Registry)  
HTA (Health Technology Assessment Database)  
CODECS (COonnaissance et Décision en Economie de la Santé)  
EconLit (American Economic Association Literature Database).

The search for unpublished studies will include:

MEDNAR/Google Scholar  
NYAM (New York Academy of Medicine)  
WorldWideScience.org  
PQDT (ProQuest Dissertations & Theses Database).

Initial keywords to be used will be:

Skin cancer, skin neoplasm, skin tumor, skin growth, non-melanoma skin cancer, NMSC, squamous cell carcinoma, SCC, basal cell carcinoma *or* BCC

*and*

Mohs, Mohs surgery, Mohs micrographic surgery, MMS, micrographic surgery *or* microsurgery

*and*

Economic, cost, cost effectiveness, CEA, cost utility, CUA, cost benefit, CBA, cost minimization, CMA, economic model, modeling, decision tree, dynamic model, state-transition model, markov model, probabilistic model, stochastic model *or* deterministic model.

### **Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers (YTJ and YX) for methodological validity prior to inclusion in the review using standardized critical appraisal instruments

from the Joanna Briggs Institute Analysis of Cost, Technology and Utilization Assessment and Review Instrument (JBI-ACTUARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer (CH or SWS). A total score of at least 6 “yes” out of the 11 critical appraisal questions will be required for studies to be included in the analysis.

## Data collection

Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-ACTUARI (Appendix II). The data extracted will include specific details about the interventions, populations, economic perspective, cost, currency, study design, economic evaluation method and outcomes of significance to the review question and specific objectives.

## Data synthesis

The findings of included studies on the costs and cost effectiveness of MMS for the range of comparators will be synthesized using narrative text, narrative tables and the JBI ACTUARI dominance ranking matrix tool. Using the dominance ranking tool, the cost effectiveness results of studies will be classified as showing strong dominance, weak dominance or non-dominance. The synthesis will include a description of the context surrounding the included evaluations and consideration of what the settings, in which the cost effectiveness results were generated, suggest about the circumstances that are conducive to MMS being more effective and less costly than the comparators. A single hierarchical decision matrix will be produced for each included outcome and where possible, the influence of the quantitative study design on the dominance ranking of MMS will be examined, by producing a separate hierarchical decision matrix for each quantitative study design.

## Conflicts of interest

None.

## Acknowledgements

None.

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**Appendix I: Appraisal instruments**  
**ACTUARI appraisal instrument**

**JBI Critical Appraisal Checklist for Economic Evaluations**

Reviewer ..... Date .....

Author ..... Year ..... Record Number .....

	Yes	No	Unclear	Not Applicable
1. Is there a well defined question?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Is there comprehensive description of alternatives?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Are all important and relevant costs and outcomes for each alternative identified?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Has clinical effectiveness been established?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Are costs and outcomes measured accurately?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Are costs and outcomes valued credibly?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Are costs and outcomes adjusted for differential timing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Is there an incremental analysis of costs and consequences?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Do study results include all issues of concern to users?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Are the results generalisable to the setting of interest in the review?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include  Exclude  Seek further info.

Comments (Including reasons for exclusion)

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



### Clinical Effectiveness Results

Study design

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Year range of primary studies

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Analysis used

---

Clinical outcome results

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### Economic Effectiveness results

Date/s of economic data

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Modeling used

---

Measure of benefits used in economic evaluation

---

Direct costs

---

Indirect costs

---

Currency

---

Statistical analysis

---

Estimated benefits used in EE

---

Cost results

---

Synthesis of costs and results

---

### Outcome category

		Clinical effectiveness		
		+	0	-
Cost	+	<input checked="" type="radio"/> A	<input type="radio"/> B	<input type="radio"/> C
	0	<input type="radio"/> D	<input type="radio"/> E	<input type="radio"/> F
	-	<input type="radio"/> G	<input type="radio"/> H	<input type="radio"/> I

Key	
	Effectiveness Cost
+	Better Lower
0	Equal Equal
-	Poorer Higher