Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:
Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin

Draft review available for public comment from April 6, 2017 to May 3, 2017.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	This important work represents a staggering amount of data synthesis. I agree that the "most striking observation is the dearth of information that is available comparing interventions for these very common cancers." This work provides a clear picture of our knowledge gaps. Congratulations!	Thank you
Peer Reviewer #1	Introduction	Please describe (with citations) the global burden of disease of keratinocyte carcinoma.	We have added this information to the introduction.
Peer Reviewer #1	Methods	Reference? for the following: "We also excluded studies enrolling fewer than 10 people total because they were unlikely to yield precise or broadly applicable conclusions." I would prefer to see a sensitivity analysis proving this point.	We were able to exclude all of these studies for other reasons (7 were not comparative between treatment nodes; 1 included only recurrent cancers; and 1 did not give an analysis for people with skin cancer). Thus this comment is no longer applicable.
Peer Reviewer #1	Methods	We excluded non-English studies, as there were very few of them and there is empirical evidence that excluding them typically has minimal acceptable. impact on conclusions, especially for mainstream clinical topics. [Ref 12] Please mention that is a controversial point (one with which I'm sure Cochrane Collaboration methodologists would take issue). Again I would prefer to see a sensitivity analysis proving this point.	First, based on the titles and abstracts we understand that non of the non-english language studies are RCTs and thus their inclusion would not affect the quantitative analyses. In addition, short of examining all papers in all databases and all languages, which is impractical (there are upwards of 25 million papers in pubmed only), one can never be exhaustive. All decisions related to the identification of the literature, from the exact search strategy to including non-english language studies have pros and cons. We do not think that our decisions are likely to introduce bias in this case; NMSC is a mainstream clinical topic, and ample empirical evidence favor the pecuniary calculation we did to exclude non-English Studies. (See for example, PMID 28420349).
Peer Reviewer #1	Results	Fig. A: 8 papers excluded due to n<10. Please state many patients with skin cancer/ types and number of lesions were represented in these 8 papers	Because we were able to exclude all of these studies for other reasons, this is no longer applicable.
Peer Reviewer #1	Results	Fig A: 41 trails were excluded due to being non-English--Please state the languages of these papers.	This information has been added to Appendix B
Peer Reviewer #1	Results	Fig A--1 paper with no treatment of interest--please state the treatment used in this paper.	This information has been added to Appendix B (Solasodine glycoalkaloids)

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Peer Reviewer #1	Discussion/ Conclusions	I find the implications of the major findings, limitations, and future research sections clearly stated. The time is ripe of delineation of clinical trial outcome core domains defined by KC patients and care givers to be included in all KC clinical trial research (e.g. via the Delphi process as done by OMERAC for psoriasis).	We have added a statement in the discussion on this point specifically. That outcomes across trials should be standardized and we encourage the development of a core outcome set as is being done for psoriasis (IDEOM) and atopic dermatitis (HOME)
Peer Reviewer #1	Clarity/Usability	The report clearly highlights new information of relevance to heath care decision making!	Thank you
Peer Reviewer #2	General Comments	This is very well done review article on a topic that is clinically ubiquitous but with high level minimal evidence. As such the review provides very little clinical utility with its analysis. In terms of the report itself, it clearly defines the target population. It creates multiple key questions, that if answered would provide tremendous value. It is well intentioned and very well done. However, it provides little clinical value, again due to the lack of current evidence.	Thank you; As we note in the report, the lack of evidence limited the clinical conclusions that could be drawn from the evidence.
Peer Reviewer #2	Introduction	On page 12 line 31, nonrandomized comparative studies are listed but the abbreviation (NRCS) is not given. This is abbreviation is referred to at a later point and would benefit from being defined here.	Thank you. We have added this abbreviation in the right places.
Peer Reviewer #2	Methods	The methods were carried out appropriately and comprehensively.	Thank you
Peer Reviewer #2	Results	The results are thorough providing what is needed and relegating the detail to the supplemental tables. There are several studies that may have been relevant especially with regards to cost but were appropriately excluded based on the inclusion criteria.	Thank you
Peer Reviewer #2	Discussion/ Conclusion	The majority of the discussion reviews the lack of evidence and the inability to draw significant conclusions. There are no new findings drawn. They do provide guidance for future trials.	Thank you
Peer Reviewer #2	Clarity and Usability	This a clear and well structured report. It begins with a coherent goal and defined population. Due to lack of evidence that meets their criteria though no significant conclusions are made. It does not change any policy or practice decisions. It also does not contribute any new information or change the understanding of the non melanoma skin cancers and their treatment.	Thank you. We believe that this systematic assessment can inform about research gaps, and about which of these represent important research needs.
Peer Reviewer #3	General Comments	Yes it addresses the range of clinical options and identifies gaps appropriately. Key questions and PICOD are easy to follow	Thank you

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Peer Reviewer #3	Introduction	This is fine	Thank you
Peer Reviewer #3	Methods	the methods in the executive summary / structured abstract are incomplete. The dual processing of the search results is not reported here, only in the full text.. As many readers may not read the full text more details are needed in the executive summary. These are clear on page 6 of the full text. Likewise the results include evidence graphs that have not been adequately described in the methods section of the executive summary. The methods section page 7 does not refer to the concept of network meta-analysis as well as it might. More details are needed. Likely also refer to the Annals of Internal medicine 2013 (Cipriani) as a good place for readers to get a better understanding.	The page limits in the executive summary do not allow us to give a detailed description.For details, we now explicitly refer readers to the main text of the report.
Peer Reviewer #3	Results	The logic flow of the presentation takes a bit to understand - or get the hang of. The use of shadow gray in the tables is helpful but no footnote is used across all the tales to remind the readers why this is used. Add a footnote to help the reader.	We have added a footnote describing the use of gray in the tables throughout the report.
Peer Reviewer #3	Discussion/ Conclusions	Given millions of cases diagnosed each year the paltry sample size of the reported randomized trials is quite amazing. How well do the hundreds of cases included represent the millions diagnosed? This needs more attention.	We have expanded on this in the limitations section of the report.
Peer Reviewer #3	Discussion/ Conclusions	the challenge of adverse events is huge in any systematic review. More discussion of the limitations of the underlying data should be added.	We have expanded on this in the limitations section of the report.
Peer Reviewer #3	Discussion/ Conclusions	Several recent reviews of meta-analyses have complained bitterly and highlighted as a weakness lack of discussion of excess significance findings in meta-analsyis (Ioannidis) and credibility ceilings (Ioannidis). Accordingly, the authors should address these issue here to avoid future negative coverage in the BMJ or other places that Ioannidis is pushing these issues on a regular basis.	We are aware of this literature. We believe that our discussion is not overinterpreting the evidence-base.
Peer Reviewer #3	Discussion/ Conclusions	I did not check against the items listed in the AMSTAR quality scale but know that umbrella reviews and critiques of systematic reviews are now using this. Again a check against this would be good preventive medicine.	We believe that we report our research accurately and completely.

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Peer Reviewer #3	Discussion/ Conclusions	finally the recommendation on gaps re more complete registry type of surveillance for these skin lesions needs to be placed more clearly in context. The volume is already afar in excess of any possible inclusion in SEER, or all State registries. Do the authors have ideas of how to reasonably provide data without bankrupting the whole surveillance process? Could just California do this (at the cost of doubling their cancer registry which is under fire - funding stress right now?) Are there other options? Should the profession cover the cost of this surveillance system?	We now acknowedge this challenge in the discussion, in the future research needs section.
Peer Reviewer #3	Clarity/Usability	The structure - organization is fine - but more details and guidance would help the reader who is not familiar with systematic review, as noted above this also applies to the evidence plots and network analysis data and presentation.	There is a tension between brevity and ability to explain concepts repeatedly and plainly. We have done our best to strike this balance in the drafting of the report. Some small changes in response to other reviewers' comments also address this issue. However, we refrain from extensive changes that would render this document even longer, and more difficult to navigate.
Peer Reviewer #4	General Comments	This review was a mammoth task and required substantial summation and synthesis. The clinical usefulness is limited, however, by pooling types of tumors for which similar treatments would almost never be considered. For example, although the paucity of studies for XRT may have led to the conclusion that surgery and radiation have similar recurrence outcomes, surgery is used in the vast majority of these tumors in the US, and X-radiation (because of its expense and poor cosmetic outcomes) is only rarely used, almost always because patients are too sick or have contraindications to surgery. Thus the statement that the data 'support' XRT seems misleading.	Thank you. We have made adjustments in the conclusions to minimize risk of overinterpretation. We have also made edits in the evidence summary to ensure that we present limitations honestly to the readers of the report.
Peer Reviewer #4	General Comments	A similar situation arises for topical drugs vs. surgery; in the vast majority of cases, the former are used for superficial tumors only.	We have edited the text to draw more attention to the fact that in the analyses, all BCCs are superficial or nodular and all SCCs are in situ. And as before, highlight heterogeneity of included patients as a limitation.
Peer Reviewer #5	General Comments	Clinical usefulness is also limited by pooling MMS and excision; together these treatments are used for the vast majority (probably c. 80%) of these cancers in the US, and a central clinical question is not whether they are superior to other treatments, but how they compare with each other.	We report these and other analogous analyses in the main report. The ES refers the interested reader to the main text.

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Peer Reviewer #6	General Comments	Our reports on our non-randomized cohort study comparing many outcomes after different treatments was described incorrectly on pages 80 and 108; the study was not limited to the VA (the majority of patients were from the private site). Similarly, the review overstates some of our results: eg, lower recurrence after MMS was not seen in propensity analyses. Similarly, the quality-of-life tool Skindex does not have 8 domains, and the qol results did not favor MMS vs. excision (ref 152, I think).	We apologize for any innacuracies. We have corrected them in this revision.
Peer Reviewer #7	General Comments	Our report of patient-reported complications after treatment of BCC and cSCC is likely relevant, but was not cited (Linos E, Wehner MR, Frosch DL, Walter L, Chren MM. Patient-reported problems after office procedures. JAMA Intern Med. 2013 Jul 8;173(13):1249-50.) I did not see what cosmetic outcome tool was used, whether it was validated, etc.	Thank you for suggesting this article. It is of interest, but was excluded from analysis because it does not give comparative data.
Public Reviewer #1	General Comments	I have reviewed this document. In the section on BCC, especially early BCC, use of radiation would be rare. This is a very common cancer, chances that regularly any practitioner would offer radiation as a primary modality for an early , not-recurrent lesion is unlikely. If there is data, it would be in a very biased, e.g. too sick to have any surgical intervention group. Lumping radiation with any surgical treatment thus is not intuitive. Adjuvant radiation, or radiation in unresectable lesions is an important modality that should be discussed.	The inclusion criteria for the RCTs that evaluated radiation did not differ substantially from those of the other RCTs included in the analysis, and the lesions are comparable except for location. Because the RCTs do not stratify the results by lesion severity and location, The NMA results do not fully account for this heterogeneity. We have noted this limitation in the discussion section of the report.
Public Reviewer #1	General Comments	Likewise a more thorough discussion of hedgehog inhibitors for lesions that are resectable with high morbidity, such as the periocular literature is also an important area of discussion.	These interventions were only reported in the studies of more advanced cancers. Because there we not enough studies to meta-analyze, these results are summarized narratively in the main report.

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Public Reviewer #1	General Comments	As for SCC, it was not well separated in the discussion from BCC and there was a lot of focus on in situ disease. In situ due to Bowen s disease is different than say the transplant population and often is not treated by plastic surgeons as they need field therapy which was discussed, e.g. 5-FU, Aldera, PDT, etc.. Technically in-situ cancer has no metastatic potential and I would at a minimum separate it from SCC more, if not remove it from the study. For SCC of the skin, a more thorough discussion of lymph node management, e.g. sentinel node biopsy should also be at least mentioned. (see as an example: JAMA Otolaryngol Head Neck Surg. 2016 Dec 1;142(12):1171-1176. Sentinel Lymph Node Biopsy for Cutaneous Squamous Cell Carcinoma on the Head and Neck. Durham AB1, Lowe L2, Malloy KM3, McHugh JB4, Bradford CR3, Chubb H1, Johnson TM5, McLean SA3.) Brian	Unfortunately, the literature was almost exclusively for in situ SCC. Of the fhe few studies that looked at SCC, only one looked at anything but SCC in situ. We make an effort to point out this lack of evidence and keep the SCC analyses in their own section.
Public Reviewer #1	General Comments	Also discussing when and which imaging modalities should be employed, is also important to discuss as they are an important component of some SCC management planning, for example a patient has clear neurotropic pain, would need a MRI, etc.. These are just some mild suggestions as the algorithm used was complex and perhaps covers the goals for this project. Sincerely,	Imaging modalities are outside of the scope of this project.
Public Reviewer #2	General Comments	The different subtypes of BCC (superficial, nodular, morpheaform) are mentioned but I am not sure they are adequately factored in. In other words, it may be considered appropriate to treat a superficial BCC with cryotherapy (I wouldn't do it) but I can't tell if the recurrence rate of that specific sub type is delineated.	The inclusion criteria for the RCTs that evaluated radiation did not differ substantially from those of the other RCTs included in the analysis, and the lesions are comparable except for location. Because the RCTs do not stratify the results by lesion severity and location, The NMA results do not fully account for this heterogeneity. We have noted this limitation in the discussion section of the report.
Public Reviewer #2	General Comments	I really think superficial RT is going to be an area of focus, some of the unsightly outcomes with external beam radiation may be lessened with a lower voltage RT, it is mentioned on page 15-no studies of effectiveness of external RT in office with portable machines (Superficial) vs RT in specialized facilities (external beam). This is important as the CPT coding of SRT is really poorly defined and if it emerges as a viable option supporting documentation will be essential as there may need to be new codes.	Thank you.

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Public Reviewer #2	General Comments	I really don't think surgical excision without immediate margin assessment and Mohs are the same thing. I know we have gone back and forth on this topic in the Quality and Performance Measurement Committee, personally I don't know of a good comparison study but if there were one I would put my money on Mohs. The point in our committee has been that a trained pathologist can look at all margins as they do in Mohs (a so called "slow Mohs"), that viewpoint seems to me to provide cover for a particular bias because slow Mohs means different things to different people but Mohs means the same to everyone. In any case, I would separate excision from Mohs.	Because the patterns were similar between specific interventions and intervention types and the data was sparse, we present only the intervention type results in the executive summary, but the individual treatment comparisons results are given in the full report
Public Reviewer #2	General Comments	Should there be any focus on cost? There is a bit of discussion on lesion size, size and location of these lesions are incredibly impactful, I think these areas require further evaluation. Specifically-nasal, ear, scalp, pretibial.	You make a good point, but cost is outside of the scope of the project.
Public Reviewer #2	General Comments	Finally, I do like the comments on immunocompromised patients and the reality that the treatment selected may be somewhat age based, in a 96-year-old patient an ED & C or topical medication may be preferred to Mohs or excision or RT.	Thank you
Public Reviewer #2	General Comments	It would be great to know the average time to recurrence of BCCs and in situ SCCs based on treatment modality	You make a good point. A sensitivity analysis of all lesions at 2 years showed similar results, though of less magnitude, so it is likely that there is some time factor. Unfortunately, this was not reported sufficiently for meta-analysis in this report.
Public Reviewer #3	Methods	data synthesis: "Arms with fewer than 5 lesions were not included in the analysis, because they contribute minimal information, and in some instances, necessitated adding model parameters that were difficult to estimate.3 I assume that "arms" here does not mean the topographical region arm of the human body, as it wouldn't make sense. On the other hand it is imbedded in a paragraph discussing topographical regions and shapes of l sions, so it could be confounded. A more exact explanation of "arms" in this specific case would maybe be appropriate	We have clarified this by adding trial before arms.
TEP Reviewer #1	General Comments	Meaningful	Thank you
TEP Reviewer #1	Introduction	Well written	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Methods	Justifiable and logical methods	Thank you
TEP Reviewer #1	Results	Details are explicit and tables clear	Thank you
TEP Reviewer #1	Discussion/ Conclusions	Discussion is meaningful; important to highlight limitations	Thank you
TEP Reviewer #1	Clarity/Usability	Very bulky in terms of usablility--need a Cliff Notes versions for dissemination	Thank you
TEP Reviewer #2	General Comments	This is an outstanding report. It is a clinically meaningful summary of the data to support what is currently the standard of care; it also highlights the lack of evidence on some important questions regarding invasive SCC	Thank you
TEP Reviewer #2	Introduction	Clearly stated	Thank you
TEP Reviewer #2	Methods	The inclusion/exclusion are justified and the methods are clearly stated. I do not have the statistical expertise to comment on whether the methods are appropriate.	Thank you
TEP Reviewer #2	Results	The results are clearly stated, the recommendation table is useful to the clinician.	Thank you
TEP Reviewer #2	Discussion/ Conclusion	The major implication here is that more research is needed. The future research section is clear at highlights important topics, but there is no discussion of the primary reason these studies have not been performed already: these cancers have not been prioritized by NCI or other funding agencies and are not captured in cancer registries. Proposing future research areas without proposing how these studies should be funded is frustrating to me as a researcher, primed and ready to perform those studies.	We have added in the discussion that given how common these tumors are and their burden on the healthcare system, research funding directed to determine the most effective and cost-effective measures for these tumors is needed. It is incumbent on funding agencies and healthcare payers to fund research examining important questions in this field.
TEP Reviewer #2	Clarity and Usability	Yes	Thank you

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TEP Reviewer #3	General Comments	Target population is explicitly defined as people with primary squamous cell and basal cell carcinoma. Subpopulations and subgroups as defined by location and grade were also examined. The authors discuss the use of primary treatment modalities, but do not mention the use of adjuvant treatment in the case of positive margins post excision, or in the case of high risk features. Would the use of postoperative radiotherapy be useful to include?	While modalities such as adjuvant RT are not within the scope of this paper, we now note that they, as well as the new drugs mentioned in line 40, have utility for BCC and SCC.
TEP Reviewer #3	Introduction	Page 11, line 40, the reference for the cost of brachytherapy should be 11 not 10 i think, please check numbering of the references.	Thank you for this comment. We have checked, and the citation is correct.
TEP Reviewer #3	Methods	The inclusion and exclusion criteria are justified. The search strategies are explicitly stated and logical, including MEDLINE, Cochrane Central Trials, Embase, clinical practice guidelines and systematic reviews. Outcomes included looking at quality of life, cosmesis, as well as costs and patient satisfaction. Given that these are largely curable cancers, these outcomes measures are important. The statistical measures are appropriate. Given the lack of studies on patients with SCC, I wonder if this could be due in part to these tumors being classified and included in studies of SCC of the head and neck rather than cutaneous SCC?	We explicitly inclued studies of SCC of the head and neck in the search, to explore exactly this issue. In the end, we excluded most of them as non-cutaneous SCC.
TEP Reviewer #3	Results	In the abstract results section the authors do not mention SCC, even if just to say there is a lack of data.	Thank you. We have added a mention of SCC to the abstract.
TEP Reviewer #3	Results	The amount of detail is appropriate; characteristics of the studies are described. Key messages are explicit and applicable; Figure, tables and appendices are adequate and describe the data well. The authors do not mention any of the studies on the use of vismodegib for advanced basal cell cancer. They mention interferon, which I have rarely seen used in clinical practice.	Information on Vismodegib is in the full report, but not in the ES because of space constraints
TEP Reviewer #3	Discussion/ Conclusion	In the discussion section page 23 (ES-14), line 9, the authors state “the results support the use of surgical and radiation treatment for low-risk BCC”. Why low – risk and not high-risk? Could the authors just state "BCC", alternately define low and high risk? The authors also mention “drug” several times in this paper – and I am not sure if they imply IV/ SC medication such as interferon – or topical drug such as imiquimod, it seems that “drug” is used to describe both.	We say low-risk because the RCTs are generally on low-risk tumors (superficial and nodular). Because of the lack of evidence, we have grouped all drugs together in a single node. Results broken down by drug type are given in the main report.

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TEP Reviewer #3	Discussion/ Conclusion	ES-15 page 24, second paragraph, the authors mention the used of external radiation therapy delivered with portable machines in the office setting – this would be applicable only in very rare cases – as the radiation that could be delivered would be very superficial and not useful for the vast majority of skin cancers. I would recommend leaving this sentence out.	The reviewer makes a good point, but we are going to keep this in because one of the motivations behind the report is the increased use of this expansive technology.
TEP Reviewer #3	Discussion/ Conclusion	The authors are correct in that there is a dearth of literature on the treatment of this very common cancer. Regarding future studies, the authors could mention the use of EGFR inhibitors such as cetuximab and erlotinib. The use of systemic treatment in the adjuvant, neoadjuvant, or metastatic setting could also be discussed.	These are generally beyond the scope of our review on primary tumors.
TEP Reviewer #3	Clarity and Usability	The report is well structured and organized, main points presented well. Conclusions are relevant. I do not think this report necessarily provides new information, but does summarize the relevant literature.	Thank you