Evidence-based Practice Center Systematic Review Protocol

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

Initial publication date: June 23, 2016
Amendment Date(s): July 27, 2016
(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Skin cancers, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common malignancies in the U.S.[1] BCC and SCC are collectively referred to keratinocyte carcinomas (KC). Over 5.4 million KC are diagnosed in 3.3 million people in the U.S. annually.[2, 3] Generally KCs are not aggressive and do not metastasize or kill as often as melanoma, which is the third most common skin cancer.[4] However, SCC can metastasize and is estimated to kill between 3900 and 8800 people in the U.S. each year.[5] Further, KC and their treatment may result in morbidity (including disfigurement and loss of function) and can adversely impact quality of life.[3] The recent Surgeon General's call to action to prevent skin cancer at the population level emphasizes the public health importance of dealing with KC.[6] Because of their frequency, KC are the fifth most expensive cancer at the population level, and, being more common in older adults, their management is of great importance to Medicare.[2, 3, 7] It is estimated that in 2012, interventions for KC were given to over 2 million Medicare beneficiaries.[2]

There are many potential management strategies for KC, and they can be broadly grouped into eight main categories: (1) surgical excision without intraoperative evaluation of the margins, (2) surgical excision with intraoperative evaluation of the margins, (3) destruction via temperature gradients, (4) ionizing radiation, (5) photodynamic interventions, (6) medical therapies, along with (7) combinations of these therapies, and (8) watchful waiting. Surgical management is used most commonly, and specific techniques include simple surgical excision with pre-specified margins, surgery with intra-operative margin control (e.g. Mohs micrographic surgery or frozen sections), and curettage, which is usually combined with secondary destruction using electrodessication.[8] Cryotherapy with liquid nitrogen is a second destructive method. Ionizing radiation modalities include traditional external beam radiation, as well as brachytherapy, in which radioactive implants are placed directly in the tumor. Topical medical treatments include topical chemotherapy (such as 5-fluorouracil), topical immunomodulatory medications (such as imiquimod), and topical photosensitizers (such as 5-aminoleveulinic acid (ALA) and methyl-ALA) that are combined with specific wavelengths of light to destroy tumor cells. New targeted systemic agents, such as vismodegib for advanced BCC,[9] are also available, but are used much less commonly than the modalities listed above. Additionally, active non-intervention (watchful waiting)

has recently been advanced as a therapeutic strategy, particularly for patients with decreased life expectancy.[10]

The choice of management strategy for an individual patient with a specific KC is complex. Factors that are important include patient factors (e.g. age, frailty, immunosuppression, and personal preference) and tumor factors (e.g. histologic subtype, size, and location). Adding to the complexity of this decisionmaking process is a lack of clarity regarding the comparative efficacy and safety of the available options.

There is general agreement that surgical removal is the gold standard, but it is not clear how other therapeutic options compare between them and with surgery, despite several dozen randomized controlled trials (RCTs) and nonrandomized comparative studies (e.g., see references[11-16]) and over 30 systematic reviews and meta-analyses (e.g., see references[17-24]). None of the existing reviews includes all treatment modalities for both BCC and SCC. The Australian and Finnish clinical practice guidelines for KC management allude to the difficulty in interpreting the existing evidence-base, which comprises comparisons among pairs of several available treatments.[25, 26] Furthermore, existing guidance is not based on systematic assessments of the evidence. It is hoped that the information in this review will be useful in the development of future guidelines, such as the guidelines on KC from the American Academy of Dermatology, anticipated later in 2016.

Interventions for treating skin cancers differ substantially in cost and have a huge economic impact.[3, 7, 27, 28] Payers are faced with increased utilization of costly therapies, such as brachytherapy, without clear evidence for relative benefits to justify increased costs.[29]

It is of the utmost importance to patients, clinicians, and payers to have reliable estimates of KC treatments' comparative effectiveness and safety with respect to patient-relevant outcomes to inform clinical decision making and payer coverage decisions. The objective of this systematic review is to comprehensively collect information on the comparative effectiveness and safety of each of the above-mentioned therapeutic strategies for both BCC and SCC. We will synthesize data on important KC-related outcomes using network meta-analysis techniques, which have heretofore not been used related to this topic, to provide the best possible estimates of the comparative benefits and harms across all treatment modalities for KC.

II. The Key Questions

With input from clinical experts, we have developed the following Key Questions (KQ) and study eligibility criteria for the systematic review update. The KQs were revised based on public comments to explicitly include only basal cell and squamous cell carcinoma of the skin.

For adult patients with basal cell and squamous cell carcinoma of the skin:

Key Question 1: What is the comparative effectiveness of various interventions, overall and in subgroups of interest?

Key Question 2: How do the adverse events associated with the various interventions compare overall and in subgroups of interest?

Eligibility Criteria

For both KQs, the Eligibility Criteria will be:

Population**:** Squamous cell carcinoma and basal cell carcinoma, primary cancers.

- Sub-populations of interest:
  - Immunocompromised
    - Post-transplant (solid organ vs. bone marrow)
    - HIV
    - Chemotherapy
    - Chronic Lymphocytic Leukemia (CLL), and other leukemias and lymphomas
    - Other iatrogenic
  - People with a limited life expectancy (e.g., the very elderly, those with terminal cancer, those with end stage renal disease)
- Subgroups defined by location or grade of lesion are also of interest:
  - Location
    - Face
    - Hands
    - Trunk/extremities
  - Subtypes
    - of BCC (e.g. superficial)
    - of SCC (e.g. keratoacanthoma or Bowen's)

Interventions

- Surgical excision without intraoperative evaluation of the margins
  - Trichloroacetic acid (TCA) plus surgical excision
- Surgery with intraoperative evaluation of the margins
  - Mohs micrographically controlled surgery
  - Other surgeries that involve intraoperative assessments
- Interventions that destroy the lesion via temperature gradients
  - Cryotherapy
  - Diathermy/electrodesiccation
  - Curettage of the lesion plus diathermy (cauterization) of margins
  - CO_2 laser therapy
- Interventions that destroy the lesion with ionizing radiation
  - External beam radiation with photons (X or gamma rays), electrons (beta rays), or positively charged particles (e.g., protons, helium nuclei/alpha rays)
    - Orthovoltage radiation treatment (commonly, for BCC)

        - Megavoltage radiation treatment (commonly, for SCC)
        - In-office radiation machines (eg. SENSUS machines)
    - Brachytherapy with superficial application or interstitial application (pleisiotherapy) of radiation sources (usually emitting beta or alpha rays)
- Photodynamic interventions
    - Methyl aminolevulinate (MAL) + red light
    - 5-aminolevulinic acid (ALA) + blue light
- Medical interventions
    - Topical 5-fluorouracil (5-FU)
    - Intralesional 5-fluorouracil (5-FU)
    - Topical methotrexate
    - Intralesional methotrexate
    - Tomical bleomycin
    - Topical imiquimod
    - Topical BEC-5 cream
    - Topical diclofenac
    - Intralesional interferon (IFN alpha-2a/2b or INF beta)
    - Topical ingenol mebutate
    - Topical vismodegib (Erivedge)
    - Topical sonidegib (Odomzo)
- Combination therapies
- Monitoring/watchful waiting

Outcomes

- Recurrence/cure rate (as defined in studies)
- Disfigurement
- Quality of Life (only if they use validated instruments to measure – e.g. Short Form Health Survey-36, Skindex, Skin Cancer Index, Skin Cancer Quality of Life Impact Tool)
- Mental health, anxiety, depression, intrusive thoughts (only if they use validated instruments to measure – e.g. State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, Impact of Event Scale)
- Patient satisfaction with treatment (only if they use validated instruments to measure – e.g. Patient Satisfaction Questionnaire-18, Skin Cancer Index patient satisfaction subscale)
- Mortality
- Resource utilization
- Adverse events, including those that are reported by patients and clinically, as well as actively and passively. Both short-term (e.g. pain, skin irritation) and long-term (e.g. radiation exposure, scarring) adverse events will be recorded.

Timing

- Any

Setting

- Any

Comments About the Eligibility Criteria

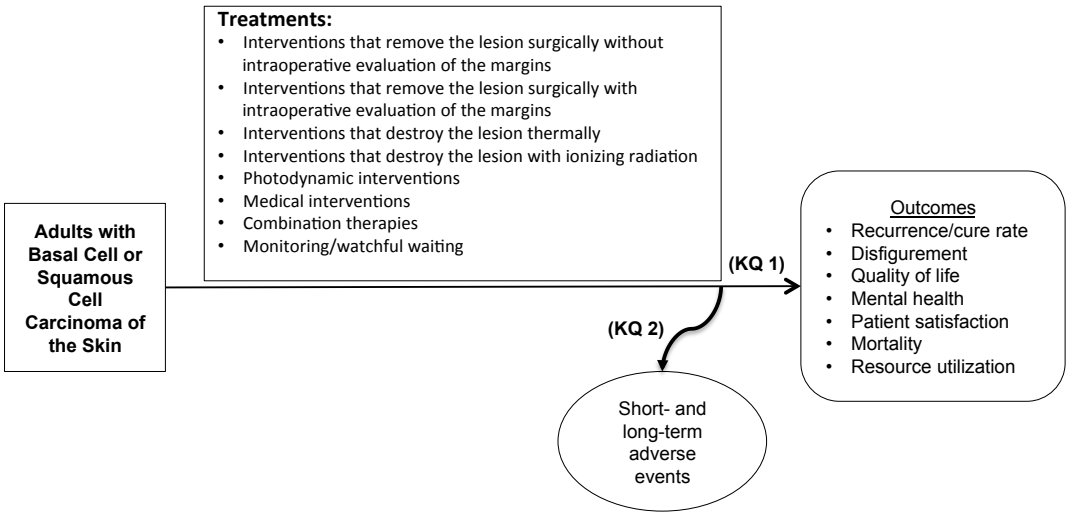
Because the key questions are about comparative effectiveness and safety, only comparative studies, including randomized controlled trials (RCTs) and nonrandomized comparative studies would be eligible. This includes placebo-controlled studies.

We will not include cancers of the genital areas or the mucosal surfaces of the lip in the analysis because they have different etiology, being associated with HPV infection, and they are treated differently. We will record the number of studies that are relevant to these areas in an evidence map.

III. Analytic Framework

To guide the assessment of studies, the analytic framework maps the specific linkages associating the populations of interest, the interventions, and outcomes of interest. The analytic framework depicts the chains of logic that evidence must support to link the studied interventions studied.

Figure 1: Analytic Framework for Treatments for Basal Cell and Squamous Cell Carcinoma of the Skin



IV. Methods

The Evidence-based Practice Center (EPC) will conduct the review based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[30]

Criteria for Inclusion/Exclusion of Studies in the Review: Please refer to Section II *The Key Questions*, where the Eligibility Criteria are listed after the KQs.

Searching for the Evidence: We will conduct literature searches of studies in PubMed, the Cochrane Central Trials Registry, the Cochrane Database of Systematic Reviews, and EMBASE to identify primary research studies meeting our criteria. These databases should adequately cover the published literature on this topic. We anticipate using the search strategy in Appendix A, adapted as needed for each database. The search strategy will be peer reviewed by an independent, experienced information specialist/librarian. We will send the Technical Expert Panel (see section X below for a description of the role of the Technical Experts) a list of included studies and ask them to provide citations of potentially relevant articles that we may have missed. Additionally, we will peruse the reference lists of published clinical practice guidelines, relevant narrative and systematic reviews, and Scientific Information Packages from manufacturers or other stakeholders. We will also search ClinicalTrials.gov for ongoing studies and studies that are not published in the medical literature. We will use existing systematic reviews primarily as sources of studies; we will extract and incorporate all studies *de novo* and will not summarize or incorporate existing systematic reviews, per se. All articles identified through these sources will be screened for eligibility, using the same criteria as was used for articles identified through literature searches. Peer and public review will provide an additional opportunity for the TEP and other experts in the field to ensure that no key publications have been missed. The search will be updated upon submission of the draft report for peer and public review.

All citations found by literature searches and other sources will be independently screened by two researchers. At the start of abstract screening, we will implement a training session, in which all researchers will screen the same articles and conflicts will be discussed. During double-screening, we will resolve conflicts as a group. All screening will be done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). All potentially relevant studies will be rescreened in full text to ensure eligibility.

Data Extraction and Data Management: Each study will be extracted by one methodologist. The extraction will be reviewed and confirmed by at least one other experienced methodologist. Any disagreements will be resolved by discussion among the team. Data will be extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key Questions. Upon completion of the review, the SRDR database will be made accessible to the general public (with capacity to read, download, and comment on data). The basic elements and design of the extraction form will be the similar to those used for other AHRQ comparative effectiveness reviews and will include elements that

address population characteristics, including method of diagnosis; descriptions of the interventions, exposures, and comparators analyzed; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions. If information is stratified by carcinoma subtype for BCC (e.g. basal-squamous carcinoma or morpheaform) and SCC (e.g. Bowen's Disease, well-differentiated, or poorly differentiated), we will record that information as well.

Assessment of Methodological Risk of Bias of Individual Studies: We will assess the methodological quality of each study based on predefined criteria. For RCTs, we will use the Cochrane risk of bias tool,[31] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we will use relevant questions from the Newcastle Ottawa Scale.[32] Quality/risk of bias issues pertinent to specific outcomes within a study will be noted and considered when determining the overall strength of evidence for conclusions related to those outcomes. To assess the number of unpublished articles, we will record the number of studies found through the clinicaltrials.gov search that are completed but unpublished.

Data Synthesis: All included studies will be summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. These included descriptions of the study design, sample size, interventions, followup duration, outcomes, results, funding source, and study quality. We will include studies found in clinicaltrials.gov that give results but do not have a published report.

We expect to conduct random effects model meta-analyses of comparative studies, if they are sufficiently similar in population, interventions, and outcomes. Specific methods and metrics (summary measures) to be meta-analyzed will depend on available, reported study data, but we expect to summarize odds ratios of the categorical outcome. Possible reasons for statistical heterogeneity will be explored qualitatively and, if appropriate data are available, we may also conduct metaregression analyses to evaluate study, patient, and intervention features and to evaluate dose-response. We will explore subgroup differences within (and possibly across) studies, including, for example different levels of immunocompromise (e.g. solid organ transplant recipients versus people living with HIV that is well controlled on HAART) or different methods of tumor diagnosis.

We also plan to conduct a network meta-analysis to compare all treatment alternatives across studies. The exact methodology to conduct the network meta-analysis has not yet been determined, but we will confer with international experts in network meta-analysis. Full methodology for conducting the network meta-analyses will be reported, as will all results and assessments of model fit, coherence, and consistency, in the methods section of the report.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: We will grade the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[30] We plan to assess the strength of evidence for each outcome. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of

any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating will be summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating

Assessing Applicability: We will assess the applicability within and across studies with reference to demographics of enrolled participants (e.g. age and sex distributions), the location and severity of the lesions, and the availability of treatments (e.g. various radiation machines).

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VI. Definition of Terms

Keratinocyte carcinomas (KC) is the collective term for basal cell carcinoma and squamous cell carcinoma of the skin.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
July 27, 2016	PICO Interventions	• Interventions that destroy the lesion via temperature gradients ○ Cryotherapy ○ Diathermy/electro desiccation ○ Curettage of the lesion plus diathermy (cauterization) of margins ○ CO_2 laser therapy	• Interventions that destroy the lesion via temperature gradients ○ Cryotherapy ○ Diathermy/elect rodesiccation ○ Curettage of the lesion plus diathermy (cauterization) of margins ○ Curettage of the lesion plus cryotherapy ○ CO_2 laser therapy	Clarification that this intervention is also eligible.
July 27, 2016	Comments about the Eligibility Criteria	N/A	Added the following statement: we will exclude studies of recurrent lesions or ones that have metastasized.	Clarification of the scope of the project.
July 27, 2016	Methods: Search Strategy	We will also search ClinicalTrials.gov for ongoing studies and studies that are not published in the medical literature.	We will also search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing studies and studies that are not published in the medical literature. In addition, we will search the FDA drugs and devices portals for unpublished data.	To ensure a more comprehensive search for unpublished data.

Date	Section	Original Protocol	Revised Protocol	Rationale
July 27, 2016	Methods: Data Synthesis	We will explore subgroup differences within (and possibly across) studies, including, for example different levels of immunocompromise (e.g. solid organ transplant recipients versus people living with HIV that is well controlled on HAART) or different methods of tumor diagnosis.	We will explore subgroup differences within (and possibly across) studies, including, for example different levels of immunocompromise (e.g. solid organ transplant recipients versus people living with HIV that is well controlled on HAART), different methods of tumor diagnosis, and different disease stages.	Clarification of how we will address various subgroups.

VIII. Review of Key Questions

AHRQ posted the Key Questions on the Effective Health Care Website for public comment. The EPC refined and finalized the Key Questions after review of the public comments, and further input from Technical Experts. This input is intended to ensure that the Key Questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

In addition, through an AHRQ project called IGNITE, patients were asked to comment on their experiences of comparative treatments. This information, along with the information from two patient KIs we talked to on the phone identified many patient-centered outcomes that were incorporated into the report.

X. Technical Experts

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA XXX I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A. Preliminary Literature Searches

PubMed

((("Bowen's Disease"[Mesh] OR bowen's Or "basal cell carcinoma" or "basal cell carcinomas" or "Carcinoma, Basal Cell"[Mesh] or BCC Or "squamous cell carcinoma" or "squamous cell carcinomas" OR "Carcinoma, Squamous Cell"[Mesh] or SCC OR ((keratinocyte* or "Keratinocytes"[Mesh]) and (carcinoma* or "Carcinoma"[Mesh])) OR "non-melanoma" OR "non melanoma" OR "nonmelanoma") NOT (Oropharynx OR Oropharyngeal neoplasms or "Oropharyngeal Neoplasms"[Mesh] OR Pharynx OR Pharyngeal neoplasms OR "Pharyngeal Neoplasms"[Mesh] or "Lung Neoplasms"[Mesh] or "Urinary Bladder Neoplasms"[Mesh] or "Uterine Cervical Neoplasms"[Mesh] or "Esophageal Neoplasms"[Mesh] or "Laryngeal Neoplasms"[Mesh]))
AND
(((Surger* or surgic*) and (excision or removal))
Or "shave removal"
Or "external beam radiation" Or "external-beam radiation"
Or brachytherap* or "Brachytherapy"[Mesh]
Or chemotherap*
OR Sensus
OR X-ray
OR "X-Ray Therapy"[Mesh]
OR radiotherapy OR "Radiotherapy"[Mesh]
Or (topical and (medications or chemotherap*))
Or observation
Or "watchful waiting"
Or ((Mohs or micrographic*) and surgery)
Or "Mohs Surgery"[Mesh]
Or Curett* or "Curettage"[Mesh]
Or diathermy or "Diathermy"[Mesh]
or cauterization or "Cautery"[Mesh]
Or Cryotherapy or "Cryotherapy"[Mesh]
Or electrodesiccation
Or ((CO2 or "carbon dioxide") and laser and therapy) Or "Laser Therapy"[Mesh]
Or plesiotherapy
Or "Methyl 5-aminolevulinate" or "methyl 5-aminolevulinate" [Supplementary Concept]
OR MALA
Or "5-aminolevulinic acid" or "Aminolevulinic Acid"[Mesh] Or ALA
Or Photodynamic or "Photochemotherapy"[Mesh] or Photochemotherap*
Or 5-fluorouracil
Or 5-FU
Or Bleomycin or "Bleomycin"[Mesh]
Or "Methotrexate"[Mesh]
Or Methotrexate
Or imiquimod or "imiquimod" [Supplementary Concept]
Or BEC-5
Or diclofenac or "Diclofenac"[Mesh]

Or interferon or IFN
Or “Ingenol mebutate” or "3-ingenyl angelate" [Supplementary Concept] or PEP005 or PEP-005 or “PEP 005”
Or Vismodegib Or Erivedge or "HhAntag691" [Supplementary Concept] or NSC747691 or NSC-747691 or “NSC 747691” or R-3616 or R3616 or “R 3616” or RG-3616 or RG3616 or “RG 3616” or GDC-0449 or GDC0449 or “GDC 0449”
Or Sonidegib or Odomzo or "LDE225" [Supplementary Concept] or NVP-LDE225
Or Itraconazole or "Itraconazole"[Mesh] or Sporanox or Orungal or R51211 or R-51211 or “R 51211”)
AND
("Cohort Studies"[Mesh] OR cohort OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR (follow-up or followup) OR longitudinal OR "Placebos"[Mesh] OR placebo* OR "Research Design"[Mesh] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Comparative Study" [Publication Type] OR ((comparative OR Intervention) AND study) OR pretest* OR pre test* OR posttest* OR post test* OR prepost* OR pre post* OR “before and after” OR interrupted time* OR time serie* OR intervention* OR ((quasi-experiment* OR quasiexperiment* OR quasi experiment*) and (method or study or trial or design*)) OR "Case-Control Studies"[Mesh] OR (case and control) OR Clinical Studies OR "Clinical Studies as Topic"[Mesh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random* OR "Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Placebos"[Mesh] OR placebo OR ((clinical OR controlled) and trial*) OR ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)) OR rct))
NOT
(“addresses”[pt] or “autobiography”[pt] or “bibliography”[pt] or “biography”[pt] or “case reports”[pt] or “comment”[pt] or “congresses”[pt] or “dictionary”[pt] or “directory”[pt] or “editorial”[pt] or “festschrift”[pt] or “government publications”[pt] or “historical article”[pt] or “interview”[pt] or “lectures”[pt] or “legal cases”[pt] or “legislation”[pt] or “letter”[pt] or “news”[pt] or “newspaper article”[pt] or “patient education handout”[pt] or “periodical index”[pt] or "comment on" or “review”[pt] or “systematic”[sb] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] or cow[tw] or cows[tw] or chicken*[tw] or horse[tw] or horses[tw] or mice[tw] or mouse[tw] or bovine[tw] or sheep or ovine or murinae)

Cochrane
((bowen’s Or bowens OR basal cell carcinoma or BCC Or squamous cell carcinoma or SCC OR keratinocyte* and carcinoma* OR “non-melanoma” OR “non melanoma” OR “nonmelanoma”) NOT (Oropharynx OR Oropharyngeal neoplasms OR Pharynx OR Pharyngeal neoplasms))
AND
(((Surger* or surgic*) and (excision or removal))
Or “shave removal”
Or “external beam radiation” Or “external-beam radiation”
Or brachytherap*
Or chemotherap*

OR Sensus
OR X-ray
OR radiotherapy
Or (topical and (medications or chemotherap*))
Or observation
Or “watchful waiting”
Or ((Mohs or micrographic*) and surgery)
Or Curett*
Or diathermy
or cauterization
Or Cryotherapy
Or electrodesiccation
Or ((CO2 or “carbon dioxide”) and laser and therapy)
Or plesiotherapy
Or “Methyl 5-aminolevulinate” or "methyl 5-aminolevulinate" or MALA
Or “5-aminolevulinic acid” or ALA
Or Photodynamic or Photochemotherap*
Or 5-fluorouracil
Or 5-FU
Or Methotrexate
Or Bleomycin
Or imiquimod
Or BEC-5
Or diclofenac
Or interferon or IFN
Or “Ingenol mebutate” or "3-ingenyl angelate" or PEP005 or PEP-005 or “PEP 005”
Or Vismodegib Or Erivedge or NSC747691 or NSC-747691 or “NSC 747691” or R-3616 or R3616 or “R 3616” or RG-3616 or RG3616 or “RG 3616” or GDC-0449 or GDC0449 or “GDC 0449”
Or Sonidegib or Odomzo or NVP-LDE225
Or Itraconazole or Sporanox or Orungal or R51211 or R-51211 or “R 51211”)

EMBASE
((bowen* OR basal cell carcinoma or BCC Or squamous cell carcinoma or SCC OR keratinocyte* and carcinoma* OR non-melanoma OR non melanoma OR nonmelanoma) NOT (Oropharynx OR Oropharyngeal neoplasms OR Pharynx OR Pharyngeal neoplasms))
AND
(((Surger* or surgic*) and (excision or removal))
Or shave removal
Or external beam radiation Or external-beam radiation
Or brachytherap*
Or chemotherap*
OR Sensus
OR X-ray

OR radiotherapy
Or (topical and (medications or chemotherap*))
Or observation
Or watchful waiting
Or ((Mohs or micrographic*) and surgery)
Or Curett*
Or diathermy
or cauterization
Or Cryotherapy
Or electrodesiccation
Or ((CO2 or carbon dioxide) and laser and therapy)
Or plesiotherapy
Or Methyl 5-aminolevulinate or MALA
Or 5-aminolevulinic acid or ALA
Or Photodynamic or Photochemotherap*
Or 5-fluorouracil
Or 5-FU
Or Bleomycin
Or imiquimod
Or Methotrexate
Or BEC-5
Or diclofenac
Or interferon or IFN
Or Ingenol mebutate or 3-ingenyl angelate
Or Vismodegib Or Erivedge
Or Sonidegib or Odomzo
Or Itraconazole or Sporanox or Orungal)
AND
(Clinical trial/
OR Randomized controlled trial/
OR Randomization/
OR Single blind procedure/
OR Double blind procedure/
OR Crossover procedure/
OR Placebo/
OR Randomi?ed controlled trial$.tw.
OR Rct.tw.
OR Random allocation.tw.
OR Randomly allocated.tw.
OR Allocated randomly.tw.
OR (allocated adj2 random).tw.
OR Single blind$.tw.
OR Double blind$.tw.
OR ((treble or triple) adj blind$).tw.
OR Placebo$.tw.
OR Prospective study/

OR Clinical study/
OR Case control study
OR Family study/
OR Longitudinal study/
OR Retrospective study/
OR Prospective study/
OR Randomized controlled trials/
OR Cohort analysis/
OR (Cohort adj (study or studies)).mp.
OR (Case control adj (study or studies)).tw.
OR (follow up adj (study or studies)).tw.
OR (observational adj (study or studies)).tw.
OR (epidemiologic$ adj (study or studies)).tw.
OR (cross sectional adj (study or studies)).tw.)

Limits: (human and english language and (adult <18 to 64 years> or aged <65+ years>))