JAMA Dermatology | Consensus Statement

Core Outcome Set for Actinic Keratosis Clinical Trials

Kelly A. Reynolds, BA; Daniel I. Schlessinger, MD; Jelena Vasic, MD; Sanjana Iyengar, MD; Yaqoob Qaseem, BA; Ramona Behshad, MD; Danielle M. DeHoratius, MD; Pablo Denes, MD, MPH; Aaron M. Drucker, MD, ScM; Leonard M. Dzubow, MD; Jeremy R. Etzkorn, MD; Catherine Harwood, PhD, MBBS, FRCP; John Y. S. Kim, MD; Erica H. Lee, MD; Gary S. Lissner, MD; Ashfaq A. Marghoob, MD; Rubeta N. Matin, PhD, MBBS, FRCP; Adam Mattox, DO; Bharat B. Mittal, MD; J. Regan Thomas, MD; Xiaolong Alan Zhou, MD, MSc; David Zloty, MD; Jochen Schmitt, MD; Jamie Kirkham, PhD; Emily Poon, PhD; Joseph F. Sobanko, MD; Todd V. Cartee, MD; Ian A. Maher, MD; Murad Alam, MD, MSCI, MBA

IMPORTANCE Although various treatments have been found in clinical trials to be effective in treating actinic keratosis (AK), researchers often report different outcomes. Heterogeneous outcome reporting precludes the comparison of results across studies and impedes the synthesis of treatment effectiveness in systematic reviews.

OBJECTIVE To establish an international core outcome set for all clinical studies on AK treatment using systematic literature review and a Delphi consensus process.

EVIDENCE REVIEW Survey study with a formal consensus process. The keywords *actinic keratosis* and *treatment* were searched in PubMed, Embase, CINAHL, and the Cochrane Library to identify English-language studies investigating AK treatments published between January 1, 1980, and July 13, 2015. Physician and patient stakeholders were nominated to participate in Delphi surveys by the Measurement of Priority Outcome Variables in Dermatologic Surgery Steering Committee members. All participants from the first round were invited to participate in the second round. Outcomes reported in randomized controlled clinical trials on AK treatment were rated via web-based e-Delphi consensus surveys. Stakeholders were asked to assess the relative importance of each outcome in 2 Delphi survey rounds. Outcomes were provisionally included, pending the final consensus conference, if at least 70% of patient or physician stakeholders rated the outcome as critically important in 1 or both Delphi rounds and the outcome received a mean score of 7.5 from either stakeholder group. Data analysis was performed from November 5, 2018, to February 27, 2019.

FINDINGS A total of 516 outcomes were identified by reviewing the literature and surveying key stakeholder groups. After deduplication and combination of similar outcomes, 137 of the 516 outcomes were included in the Delphi surveys. Twenty-one physicians and 12 patients participated in round 1 of the eDelphi survey, with 17 physicians (81%) retained and 12 patients (100%) retained in round 2. Of the 137 candidate outcomes, 9 met a priori Delphi consensus criteria, and 6 were included in the final outcomes set after a consensus meeting: complete clearance of AKs, percentage of AKs cleared, severity of adverse events, patient perspective on effectiveness, patient-reported future treatment preference, and recurrence rate. It was recommended that treatment response be assessed at 2 to 4 months and recurrence at 6 to 12 months, with the AK rate of progression to cutaneous squamous cell carcinoma reported whenever long-term follow-up was possible.

CONCLUSIONS AND RELEVANCE Consensus was reached regarding a core outcome set for AK trials. Further research may help determine the specific outcome measures used to assess each of these outcomes.

Editorial page 255

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Murad Alam, MD, MSCI, MBA, Department of Dermatology, Feinberg School of Medicine, Northwestern University, 676 N St Clair St, Ste 1600, Chicago, IL 60611 (m-alam@northwestern.edu).

JAMA Dermatol. 2020;156(3):326-333. doi:10.1001/jamadermatol.2019.4212
Published online January 15, 2020.

Treatment of actinic keratosis (AK) is recommended to reduce the risk of progression to invasive cutaneous squamous cell carcinoma (SCC).[1] Topical and mechanical interventions evaluated in clinical trials for AK include spot treatments for isolated lesions (eg, cryotherapy, trichloroacetic acid, and electrodessication and curettage) and field therapy for more widespread disease (eg, topical chemotherapies, chemical peels, and photodynamic therapy).[1,2] Currently, approximately 300 studies on AK are registered on ClinicalTrials.gov as recruiting, ongoing, or completed.[3]

The heterogeneity of safety and effectiveness outcomes reported in research studies of AK treatments[4] impedes the comparison of results across trials and between different treatment modalities. Lack of outcome standardization may also contribute to selective reporting bias, which may skew estimates of treatment effectiveness.[5]

Development of core outcome sets (COSs) has been promoted as a method by which to increase the utility and generalizability of research trials. Core outcome sets are an agreed-on minimum set of outcomes that are recommended to be measured and reported in all studies of a given condition.[6] Widespread adoption of COSs would standardize outcome reporting in clinical trials and facilitate evidence synthesis of treatment effectiveness and safety in systematic reviews, meta-analyses, and treatment guidelines.[6] Of note, the use of COSs does not restrict the number of additional outcomes that may be measured in a clinical trial. Although several dermatology-specific COSs have been developed in recent years,[7-14] there is no existing COS for treatment of AK.

The objective of this study was to develop an international COS for clinical trials of treatment of AK. This goal was achieved by conducting a systematic literature review and stakeholder survey to develop a list of possible outcomes, narrowing this to a short list, and identifying a COS through Delphi consensus followed by an in-person consensus conference. The conceptual framework of this method was set forth by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative[15,16] and the Cochrane Skin Group Core Outcomes Set Initiative (CSG-COUSIN) methods groups.[17,18]

Key Points

Question What are the most important outcomes to report in clinical trials on actinic keratosis?

Findings In this survey study including physician and patient stakeholders (33 in round 1 and 29 in round 2), a consensus was reached regarding a core set of 6 of 137 outcomes and domains of actinic keratosis: complete clearance of actinic keratoses, percentage of actinic keratoses cleared, severity of adverse events, patient perspective on effectiveness, patient-reported future treatment preference, and rate of recurrence.

Meaning In studies of treatment of actinic keratosis, the recommended core outcomes should be reported as a minimum to facilitate comparison of results across studies.

Methods

Literature Review

For this survey study, PubMed, Embase, CINAHL, and the Cochrane Library were searched to identify English-language studies investigating AK treatments published between January 1, 1980, and July 13, 2015. Search terms included *actinic keratosis* and *treatment* (eTable in the Supplement). Screening of article titles and abstracts was completed by 2 reviewers (D.I.S., S.I.). Full-text review of the remaining studies was independently performed by 2 research team members (J.V., D.I.S.). Inclusion criteria for the studies included were as follows: (1) randomized design evaluating at least 1 AK treatment modality, (2) at least 10 individuals in the treatment arm(s), and (3) reporting of at least 1 safety, effectiveness, or patient-reported outcome. Disagreements pertaining to study inclusion were resolved by adjudication of the Measurement of Priority Outcome Variables in Dermatologic Surgery (IMPROVED) Steering Committee (J.F.S., T.V.C., I.A.M, and M.A.). To avoid duplication, the COMET and CSG-COUSIN databases were queried for any AK COSs under development before initiation of this project. A total of 516 outcomes were identified through reviewing the literature and surveying key stakeholder groups. Data analysis was performed from November 5, 2018, to February 27, 2019. The protocol for development of this COS was registered with COMET and CSG-COUSIN.[19,20] All participants provided written informed consent, and all data were deidentified. Data collection using the Delphi process was approved by the Northwestern University Institutional Review Board. This document is in accordance with the Core Outcome Set Standards for Reporting (COS-STAR) checklist.[21]

IMPROVED Steering Committee

The IMPROVED Steering Committee focuses specifically on developing COSs for dermatologic diseases or conditions that may be treated procedurally. All COS development projects initiated by IMPROVED are in accordance with the process recommendations set forth by the COMET Initiative[15] and the CSG-COUSIN methods group.[17] Additional guidance has been derived from the Harmonising Outcome Measures for Eczema roadmap.[18]

Outcome Extraction

Three researchers (J.V., S.I., Y.Q.) independently extracted all reported outcomes from each of the included studies. Additional outcomes were sought by surveying other key stakeholders, including nonphysician health care professionals (nurse practitioners and physician assistants), regulatory personnel, pharmacologists, and industry scientists. After a comprehensive list of outcomes was produced, the list was deduplicated, and similar items were collapsed by 2 steering committee members (J.F.S., I.A.M.). Disagreements were resolved by forced agreement after inclusion of a third steering committee member (M.A.). Similar outcomes were then categorized into higher-level domains (categories of related outcomes used for organization of the Delphi surveys) (similar to the methods from previous COS publications[13,18,22]) by 2 reviewers (K.A.R., E.P.).

Patient and Physician Stakeholders

Patients with a history of AK were recruited from 6 dermatology clinics located in the Midwest and Northeast regions of the United States. International and US physician stakeholders were identified and recruited by IMPROVED Steering Committee members based on the following criteria: prior involvement in COS development and/or expertise with AK through clinical management or a previous publication on AK. Physicians with known or disclosed potential con-

flicts of interest that may have resulted in conscious or subconscious bias in their Delphi ratings (eg, developers of a specific outcome measures or those who may have benefited from the inclusion of specific outcomes in the core set) were excluded. Physician and patient stakeholders were formally invited to participate via email. Stakeholders who completed the first round were eligible to participate in the second round of Delphi surveys.

Demographic information, including age, sex, and level of education, was obtained from all patients who consented. Specialties and geographic locations of participating physician stakeholders were also noted.

Delphi Consensus Method

The condensed long list of outcomes was presented for rating through web-based eDelphi consensus surveys (eAppendix in the Supplement).[23] Care was taken in preparing the Delphi items to not excessively editorialize or reword the work product emanating from literature review and expert consensus because rewording can introduce unintended bias.

After stakeholders indicated their intent to participate in the eDelphi process, participants were contacted by a member of the research team who provided background information regarding the study, described the importance of outcomes in research, and explained the nature of the Delphi consensus method. Participants were also directed to a video created by the COMET group for additional background (https://www.youtube.com/watch?v=g1MZi2mzK1U). Three days before the eDelphi survey was available online, instructions for completing the survey were given via email or telephone, whichever the participants preferred. Participants were encouraged to call when they were logged into the Delphi survey so that additional instructions or clarifications could be provided in real time.

Stakeholders were asked to rate the relative importance of each of the outcomes on a scale of 1 to 9 as not important (score of 1-3), important but not critical (score of 4-6), or critically important (score of 7-9). Physician and patient stakeholders were also allowed to choose unable to score for any outcomes on which they did not wish to comment. Furthermore, lay descriptions appeared above each outcome as the participant hovered over the relevant outcome item in the eDelphi software.

The eDelphi surveys were completed in 2 prespecified rounds with a contingency plan to repeat the Delphi rounds if inadequate consensus was reached after 2 rounds, as defined as an officially sanctioned method from the COMET group.[24] In the first eDelphi round, stakeholders rated the importance of each of the outcomes and were encouraged to add additional outcomes not in the original list. Between rounds 1 and 2, all participants were contacted via telephone and email to confirm their willingness to participate in the second round, elicit feedback about their survey experience, and ensure that any questions they had pertaining to the process were addressed. Physician and patient stakeholder responses from round 1 were summarized using descriptive statistics and distributed back to stakeholders in round 2, at which point they were asked to rerate the importance of each of the outcomes in light of the group responses.

Any narrative comments provided in the eDelphi survey in the first round were collected and transferred to an Excel spreadsheet (Microsoft). All comments except those that merely reiterated how strongly they felt (eg, "This is very important.") or conveyed uncertainty regarding the definition of a candidate outcome (eg, "What is meant by X?") were included in the eDelphi software during the second round. Specifically, these comments were appended to relevant items and were visible when participants hovered their cursor over that item.

The second round of surveys contained the same set of outcomes as the first round as well as all additional outcomes that were proposed in round 1. Unequal numbers in the patient and physician groups did not affect the weighting of results because statistics were calculated separately for both stakeholder groups.

Outcomes were considered for inclusion in the final core set if at least 70% of physician or patient stakeholders rated them as critically important and the mean score in either stakeholder group was 7.5 or greater. Outcomes that achieved minimum 70% consensus in either stakeholder group with scores between 6.5 and 7.5 were able to be introduced for consideration by participants at the in-person consensus meeting. Outcomes with scores less than 6.5 in both groups or that achieved less than 70% consensus among patient and physician stakeholders were excluded from consideration for inclusion in the COS. These cutoffs for consensus were based on other COS publications[13,18,25-27] and were chosen a priori.

Consensus Meeting

The results of the eDelphi surveys were discussed and voted on at an in-person consensus meeting convened in March 2019. All stakeholders, including Delphi participants and members of the steering committee, were invited to participate. Participant votes were weighted equally.

Statistical Analysis

Statistical analyses were performed in SAS Studio, version 3.7 (SAS Institute Inc).

Results

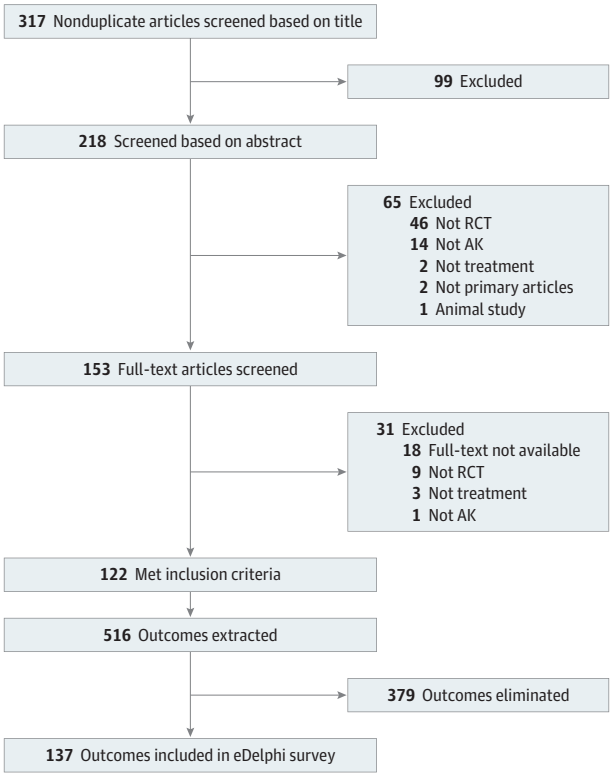
Literature Search and Outcome Extraction

A total of 317 articles were identified from the literature search, of which 99 were excluded after title review, 65 based on abstract screening, and 31 after full-text review (**Figure 1**). A total of 516 unique outcomes were extracted from the remaining 122 articles. After deduplication and collapsing of similar outcomes by steering committee members (J.F.S., I.A.M.), 137 unique outcomes were included in the eDelphi surveys. Outcomes were categorized into 1 of the following domains (both domain titles and the outcomes listed within domains were included as individual outcomes to be rated in the Delphi surveys): clinical assessment of lesion(s) (n = 35), treatment effectiveness (n = 17), histopathologic assessment (n = 19), oncogenes (n = 12), safety and tolerability of treatment (n = 9), patient satisfaction (n = 20), procedural factors (n = 9), recurrence-free survival (n = 11), systemic effects of treatment (n = 1), and treatment adherence (n = 4).

eDelphi Participants (Stakeholders)

Invitations to participate in the eDelphi survey were distributed to 24 patients and 31 physicians, of whom 12 patients (50%) and 21 physicians (68%) participated in round 1. The same individuals were in-

Figure 1. Systematic Literature Search and Outcome Identification



AK indicates actinic keratosis; RCT, randomized clinical trial.

vited again to participate in round 2, and all 12 patient stakeholders (100%) and 17 physician stakeholders (81%) completed the second round of surveys. Stakeholders' demographic and occupational information are summarized in **Table 1**.

International eDelphi

Round 1 was completed in November 2018, with 3 participants (9%) providing narrative feedback regarding specific Delphi items, followed by invitations for round 2, which was completed in February 2019. Of the 137 outcomes that were included in the eDelphi surveys, a total of 9 outcomes met the a priori inclusion criteria for mean score and consensus regarding importance: percentage of AKs cleared, complete clearance of AKs, progression of AK to SCC, rate of recurrence, incidence of SCC, severity of adverse events, patient-reported future treatment preference, patient perspective on effectiveness, and quality of life (**Table 2**). Consensus was achieved in both the physician and patient groups for percentage of AKs cleared, complete clearance of AKs, rate of recurrence, patient perspective on effectiveness, and patient-reported future treatment preference.

Seven additional items were rated between 6.5 and 7.5 and met the consensus threshold: allergic reaction, pain, number of clinically apparent AKs, cosmetic outcome, treatment discontinuation, dosage adherence, and cost. There were no outcomes that met the criteria in the systemic effects of treatment, oncogenes, or histopathologic assessment domains.

Table 1. Demographic Characteristics of Actinic Keratosis eDelphi Survey Participants Who Completed Rounds 1 and 2

Characteristic	Participants[a]
Patient stakeholders	12 (100)[b]
Age, mean (SD), y	66.5 (7.6)
Sex	
Male	8 (67)
Female	4 (33)
Fitzpatrick skin type[c]	
I	2 (17)
II	6 (50)
III	3 (25)
IV	1 (8)
Ethnicity[c]	
Hispanic or Latino	0
Not Hispanic or Latino	12 (100)
Educational level[c]	
High school diploma	3 (25)
Bachelor's degree, BA or BS	4 (33)
Master's degree	1 (8)
Doctoral degree	4 (33)
US region	
Midwest	9 (75)
Northeast	3 (25)
Physician stakeholders	17 (81)[b]
Specialty	
General dermatology	6 (35)
Dermatologic surgery	6 (35)
Other specialties	5 (29)
Geographic location	
United States	13 (76)
Canada	2 (12)
Europe	2 (12)

[a] Data are expressed as number (percentage) of stakeholders unless otherwise indicated.

[b] Expressed as a percentage of the number of stakeholders who participated in round 1 of the eDelphi.

[c] Patient reported.

Consensus Meeting

A total of 9 international experts (43%) in general dermatology, skin cancer, dermatologic surgery, and systematic review methods and 1 patient (8%) participated in the consensus meeting in person or remotely. The 9 items that met a priori consensus criteria were discussed and voted on anonymously by all persons in attendance to be included or not included in the final core set (Table 2). After the acquiescence of most participants, the additional 7 outcomes receiving mean lower scores (>6.5) but still meeting the consensus threshold were also discussed at the meeting and were deemed eligible to be nominated into the final core set. Voting results were iteratively summarized in real time and discussed among the group until group consensus was reached.

Stakeholders agreed that severity of adverse events should be included as an outcome in the final core set. Special attention should be given to pain and local allergic reactions, which also received relatively high ratings (mean physician scores, 7.32 for pain and 7.13 for

Table 2. Outcomes Voted on in Consensus Meeting for Inclusion in Final Core Outcome Set Based on Delphi Results[a]

Domain, Outcome	Physicians (n = 17)		Patients (n = 12)	
	Mean Score (SD)	Critically Important, %	Mean Score (SD)	Critically Important, %
Treatment effectiveness				
Percentage of AKs cleared[b]	7.58 (1.33)	82	8.00 (2.31)	83
Complete clearance of AKs[b]	7.54 (1.47)	79	7.73 (1.83)	83
Recurrence-free survival				
Progression of AK to SCC	8.13 (1.04)	97	7.52 (2.23)	67
Rate of recurrence[b]	7.66 (1.30)	71	8.04 (1.24)	79
Incidence of SCC	7.58 (1.11)	89	7.10 (2.26)	54
Safety and tolerability of treatment				
Severity of adverse events[b]	7.63 (1.26)	89	6.35 (2.31)	63
Pain	7.32 (1.09)	82	5.54 (2.52)	38
Allergic reaction	7.13 (1.58)	76	6.74 (2.36)	71
Patient satisfaction				
Patient perspective on effectiveness[b]	7.05 (1.63)	79	7.50 (1.38)	71
Patient-reported future treatment preference[b]	7.21 (1.17)	74	7.50 (1.62)	79
Quality of life	7.55 (1.11)	79	6.67 (2.48)	63
Clinical assessment				
No. of clinically apparent AKs	7.05 (1.36)	76	7.04 (1.58)	54
Cosmetic outcome	6.98 (1.42)	71	6.14 (2.34)	38
Treatment adherence				
Treatment discontinuation	7.11 (1.52)	79	5.58 (2.80)	33
Dosage adherence	7.00 (1.71)	79	6.60 (2.82)	54
Procedural factors				
Cost	7.32 (1.09)	87	4.81 (2.44)	29

Abbreviations: AK, actinic keratosis; SCC, squamous cell carcinoma.

[a] Outcomes were eligible for inclusion in the final core outcome set and were discussed at the consensus meeting if at least 70% of physician or patient stakeholders rated the outcome as critically important and the outcome received a mean score greater than 6.5 in 1 or both stakeholder groups.

[b] Outcomes were included if more than 50% of consensus meeting participants voted in favor of inclusion of the outcome in the final core set.

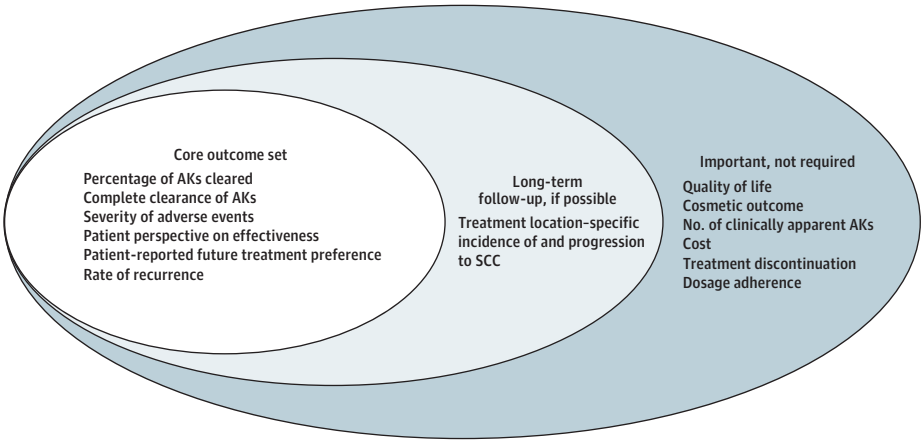
local allergic reactions). Within the domain of treatment effectiveness, participants agreed that complete clearance of AKs should be included in the final set, as should a second measure of percentage of AKs cleared. Because short-term adverse events, such as dermatitis, edema, and erythema, may obscure treatment results, it was recommended that effectiveness outcomes be measured at 2 to 4 months, a duration sufficiently long to ensure that treatment-associated inflammation had resolved but not so long as to be infeasible or to allow new, unrelated AKs to arise in the treatment field.

All stakeholders agreed that a patient-reported outcome must be part of the core set. Furthermore, consensus meeting participants concurred that patient scores should be strongly considered in selecting the relevant patient-reported outcome. However, quality of life, which met the a priori inclusion criteria based on physician ratings (mean [SD] physician score, 7.55 [1.09]; consensus level, 79%), received lower patient ratings (mean [SD] patient score, 6.67 [2.48]; consensus level, 63%). Within the patient satisfaction domain, the highest patient scores were associated with the outcomes patient perspective on effectiveness (mean [SD] patient score, 7.50 [1.38]; consensus, 71%) and patient-reported future treatment preference (ie, which treatment a patient would choose in the future if additional treatment was required) (mean [SD] patient score, 7.50 [1.62]; consensus, 79%), and these outcomes also achieved consensus among both stakeholder groups. The consensus meeting participants agreed that these outcomes would be informative, especially in head-to-head trials of 2 or more treatment interventions. Thus, patient perspective on treatment effectiveness and patient-reported future treatment preference were determined to be critically important patient-reported outcomes based on the results of the Delphi exercise and were voted into the final core set over quality of life.

Rate of recurrence was expanded to also include assessment of long-term remission and was added to the core set. Ideally, recurrence would be assessed no sooner than 6 to 12 months after treatment, and admittedly, such measurement may be difficult given the possible occurrence of new, unrelated AKs in the treatment field over time. Although consensus meeting participants also recommended that the incidence of new SCCs in the treatment area should be measured whenever even longer-term follow-up was possible, they acknowledged the difficulty posed to researchers by including a core outcome that requires long-term follow-up. Therefore, they decided that this outcome should not be included in the core set. Outcomes from other domains that reached consensus but had slightly lower mean scores (number of clinically apparent AKs, treatment discontinuation, cosmetic outcome, dosing adherence, and cost) were accepted by the meeting participants as important but not required in all clinical trials.

The final core set thus included the following outcomes: complete clearance of AKs, treatment percentage of AKs cleared, severity of adverse events, patient perspective on effectiveness, patient-reported future treatment preference (ie, which treatment a patient would choose if additional treatment was required in the future), and

Figure 2. Onion Model of Core Outcome Set for Actinic Keratosis (AK) Trials



The innermost circle includes the 6 core outcomes to be measured in all research studies on AK treatment. When long-term follow-up is possible, treatment location–specific incidence of and progression to squamous cell carcinoma (SCC) should be reported (middle ring), although this is not required in all studies. The outermost ring represents items that may be important to measure, depending on the objectives of the study, but are not required. Structure of this model is based on the OMERACT Onion.[28]

recurrence rates. Treatment location-specific incidence of and progression to SCC should be reported whenever long-term follow-up is possible but may not be practical in some clinical trials (Table 2 and Figure 2).[28]

Consensus meeting participants also considered the potential burden to researchers of measuring 6 core outcomes or domains. They suggested that the 2 patient-reported outcomes may be measured by a single instrument, that adverse event severity may be measurable on a single Likert-type scale, and that lesion recurrence, although highly desirable to include, may be infeasible to assess in shorter studies.

Discussion

This AK COS is composed of outcomes related to the safety and effectiveness of AK treatments, which received the highest ratings from an international group of expert practitioners and researchers and were also deemed important by patient participants from several centers. Several of the chosen outcomes were domain-level outcomes and, thus, broad and widely relevant. Having a COS with a broad scope is particularly relevant for a condition such as AK for which many diverse medical and procedural therapies exist.

The development of this COS was strengthened by the involvement of patient participants in the Delphi process. The involvement of patients has been emphasized by COS development agencies in recent years.[15,29-32] The generalizability of this COS was further enhanced by the involvement of an international group of general dermatologists, skin cancer specialists, dermatologic surgeons, and nondermatologist physicians from areas with patients at high risk for AK, such as the United States, Canada, and Europe.

Among effectiveness outcomes, the results of the Delphi process revealed that lesion clearance, lesion progression, and lesion recurrence are viewed as critically important by practitioners and patients. These results are consistent with the results of previous observational studies in which progression of AK to SCC was perceived as a seriously unfavorable outcome that may negatively affect quality of life.[33,34] Of interest, quality of life, cosmetic outcomes, and adverse events received lower patient ratings than physician scores. Given that many of the patients who participated in the eDelphi also had a history of skin cancer, it is possible that these low ratings were attributable to patients' perceived importance of AK treatment outcomes compared with their experience with more intensive treatments for invasive skin cancer, such as cutaneous SCC. In prior work,[33] nonmelanoma skin cancer was associated with significantly lower quality-of-life ratings compared with AK. The lesser patient concern about adverse outcomes may be attributable to the low incidence of AK treatment-related adverse events experienced by patients involved in the Delphi exercise.

The COS was agreed on by an expert group of physicians and patients based not only on the importance of the items but also on the feasibility of reporting specific outcomes in all clinical trials of AK. This feasibility of COS development is nontrivial, given that the likelihood of implementation of a COS is contingent on its usability.[15,16] Among the outcomes deemed to be important but difficult to measure in all research settings were cost and cost-effectiveness.[35] Likewise, incidence of and progression to SCC were understood to be exceedingly challenging to assess in studies that lasted a few months or a year, when only short- or medium-term follow-up is possible. However, development of SCC is particularly pertinent in longitudinal and retrospective studies, which may help frame the effectiveness of AK treatments based on the risk of subsequent SCC. Although a Cochrane review[4] found no data supporting an association of reduction of SCC incidence with AK treatment, this is unsurprising in view of the brevity of most clinical trials because of challenges pertaining to patient adherence and resource sufficiency. Evidence suggests that certain AK treatments, including fluorouracil and nicotinamide, may be effective chemopreventive strategies for reducing the risk of nonmelanoma skin cancer, but more studies are needed to elucidate whether these treatments mitigate the transformation of specific AK lesions into SCC.[36,37]

Limitations

This COS is limited by the inclusion of only outcomes reported in English-language trials, which were then surveyed among English-speaking patients and physicians. Although a considerable proportion of Delphi survey participants were patients, we would have benefited from additional patient input at the final consensus meeting.

Conclusions

Although numerous outcome measures can be explored in studies related to treatment of AK, Delphi consensus determined that a set of 6 core outcomes should ideally be reported in all studies to help facilitate comparison of results across studies. This study establishes what should be measured in AK trials; next steps for research include the development of a set of core outcome measures to further standardize how these outcomes should be addressed.

ARTICLE INFORMATION

Accepted for Publication: October 29, 2019.

Published Online: January 15, 2020. doi:10.1001/jamadermatol.2019.4212

Author Affiliations: University of Cincinnati College of Medicine, Cincinnati, Ohio (Reynolds); Department of Dermatology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Reynolds, Schlessinger, Qaseem, Zhou, Poon, Alam); Division of Dermatology, College of Medicine Tucson, University of Arizona, Tucson, Arizona (Vasic); Department of Dermatology, West Virginia University, Morgantown (Iyengar); Department of Dermatology, St Louis University, St Louis, Missouri (Behshad); Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia (DeHoratius, Etzkorn); Division of Cardiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Denes); Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada (Drucker); Division of Dermatology, Department of Medicine, Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada (Drucker); Private practice, Media, Pennsylvania (Dzubow); Department of Dermatology, Royal London Hospital, Barts Health National Health Service Trust, London, United Kingdom (Harwood); Blizard Institute, Barts and the London School of Medicine and Dentistry, Centre for Cutaneous Research and Cell Biology, Queen Mary University of London, London, United Kingdom (Harwood); Division of Plastic and Reconstructive Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Kim); Department of Dermatology, Memorial Sloan Kettering Cancer Center, New York City, New York (Lee, Marghoob); Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Lissner); Department of Dermatology, Churchill Hospital, Oxford, United Kingdom (Matin); Department of Dermatology, University of Minnesota, Minneapolis (Mattox, Maher); Department of Radiation Oncology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Mittal); Department of Otolaryngology–Head and Neck Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Thomas, Alam); Department of Dermatology & Skin Science, University of British Columbia, Vancouver, British Columbia, Canada (Zloty); Center for Evidence-Based Healthcare, Carl Gustav Carus, TU Dresden, Dresden, Germany (Schmitt); Department of Biostatistics, University of Liverpool, Liverpool, United Kingdom (Kirkham); Department of Dermatology, Perelman Center for Advanced Medicine, Hospital of the University of Pennsylvania, Philadelphia (Sobanko); Division of Dermatologic Surgery, Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia (Sobanko); Department of Dermatology, Penn State Health, Milton S. Hershey Medical Center, Hershey, Pennsylvania (Cartee); Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (Alam).

Author Contributions: Dr Alam had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Iyengar, Denes, Schmitt, Poon, Sobanko, Cartee, Maher, Alam.
Acquisition, analysis, or interpretation of data: Reynolds, Schlessinger, Vasic, Iyengar, Qaseem, Behshad, DeHoratius, Drucker, Dzubow, Etzkorn, Harwood, Kim, Lee, Lissner, Marghoob, Matin, Mattox, Mittal, Thomas, Zhou, Zloty, Schmitt, Kirkham, Poon, Cartee, Maher, Alam.
Drafting of the manuscript: Reynolds, Etzkorn, Maher, Alam.
Critical revision of the manuscript for important intellectual content: Schlessinger, Vasic, Iyengar, Qaseem, Behshad, DeHoratius, Denes, Drucker, Dzubow, Harwood, Kim, Lee, Lissner, Marghoob, Matin, Mattox, Mittal, Thomas, Zhou, Zloty, Schmitt, Kirkham, Poon, Sobanko, Cartee, Maher, Alam.
Statistical analysis: Reynolds, Schlessinger, DeHoratius, Kirkham.
Obtained funding: Alam.
Administrative, technical, or material support: Reynolds, Vasic, Iyengar, Qaseem, Zhou, Poon.
Supervision: Reynolds, Iyengar, Kirkham, Cartee, Maher, Alam.

Conflict of Interest Disclosures: Dr Drucker reported serving as an investigator for and receiving research funding from Sanofi and Regeneron; being a consultant for Sanofi, RTI Health Solutions, Eczema Society of Canada, and Canadian Agency for Drugs and Technology in Health; and receiving honoraria from Prime Inc, Spire Learning, CME Outfitters, Eczema Society of Canada, and the Canadian Dermatology Association; his institution has received educational grants from Sanofi and AbbVie. Dr Etzkorn reported receiving grants from the Dermatology Foundation during the conduct of the study. Dr Harwood reported personal fees from Sanofi and Roche outside the submitted work. Dr Lee reported receiving personal fees from UptoDate outside the submitted work. Dr Schmitt reported receiving grants from Novartis, Pfizer, ALK, and Sanofi and personal fees from Novartis and Sanofi outside the submitted work. Dr Alam reported receiving personal fees from Pulse Biosciences outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by departmental research funds from the Department of Dermatology, Northwestern University; Merz Center for Quality and Outcomes Research in Dermatologic Surgery; and the IMPROVED (Measurement of Priority Outcome Variables in Dermatologic Surgery) Group.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Lebwohl M. Actinic keratosis. *JAMA*. 2016;315(13):1394-1395. doi:10.1001/jama.2016.3065

2. Rossi R, Mori M, Lotti T. Actinic keratosis. *Int J Dermatol*. 2007;46(9):895-904. doi:10.1111/j.1365-4632.2007.03166.x

3. ClinicalTrials.gov. National Institute of Health US National Library of Medicine.https://clinicaltrials.gov/. Accessed March 12, 2019.

4. Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database Syst Rev*. 2012;12:CD004415.

5. Kirkham JJ, Dwan KM, Altman DG, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ*. 2010;340:c365. doi:10.1136/bmj.c365

6. Clarke M, Williamson P. Core outcome sets and trial registries. *Trials*. 2015;16:216. doi:10.1186/s13063-015-0738-6

7. Thorlacius L, Ingram JR, Villumsen B, et al; HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC). A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. *Br J Dermatol*. 2018;179(3):642-650. doi:10.1111/bjd.16672

8. Thiboutot D, Layton A, Chren M, et al. Acne core outcomes research network: progress in core outcome set development in clinical trials. *J Invest Dermatol*. 2018;138:S96-S96. doi:10.1016/j.jid.2018.03.574

9. Thomas KS. The BJD is embracing core outcome set development: why this is good news. *Br J Dermatol*. 2018;178(2):326-327. doi:10.1111/bjd.16229

10. Kottner J, Jacobi L, Hahnel E, et al; International Cochrane Skin Group Core Outcome Set Initiative (CSG-COUSIN) group. Core outcome sets in dermatology: report from the second meeting of the International Cochrane Skin Group Core Outcome Set Initiative. *Br J Dermatol*. 2018;178(4):e279-e285. doi:10.1111/bjd.16506

11. Horbach SER, van der Horst CMAM, Blei F, et al; OVAMA Consensus Group. Development of an international core outcome set for peripheral vascular malformations: the OVAMA project. *Br J Dermatol*. 2018;178(2):473-481. doi:10.1111/bjd.16029

12. Ingram JR, Hadjieconomou S, Piguet V. Development of core outcome sets in hidradenitis suppurativa: systematic review of outcome measure instruments to inform the process. *Br J Dermatol*. 2016;175(2):263-272. doi:10.1111/bjd.14475

13. Callis Duffin K, Merola JF, Christensen R, et al. Identifying a core domain set to assess psoriasis in clinical trials. *JAMA Dermatol*. 2018;154(10):1137-1144. doi:10.1001/jamadermatol.2018.1165

14. Eleftheriadou V, Thomas K, van Geel N, et al; Vitiligo Global Issues Consensus Group. Developing core outcome set for vitiligo clinical trials: international e-Delphi consensus. *Pigment Cell*

Melanoma Res. 2015;28(3):363-369. doi:10.1111/pcmr.12354

15. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. *Trials*. 2017;18(suppl 3):280. doi:10.1186/s13063-017-1978-4

16. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132. doi:10.1186/1745-6215-13-132

17. CSG-COUSIN Methods Group. Guidance on how to develop a core outcome set for skin disease by the CSG-COUSIN methods group. Version 2.1. https://www.uniklinikum-dresden.de/de/das-klinikum/universitaetscentren/zegv/cousin/cousin_guidance_version_2-1.pdf. Updated December 14, 2017. Accessed February 27, 2019.

18. Schmitt J, Apfelbacher C, Spuls PI, et al. The Harmonizing Outcome Measures for Eczema (HOME) roadmap: a methodological framework to develop core sets of outcome measurements in dermatology. *J Invest Dermatol*. 2015;135(1):24-30. doi:10.1038/jid.2014.320

19. COMET Initiative. Core outcome set for actinic keratosis. http://www.comet-initiative.org/studies/searchresults?guid=be343b10-f9b9-46fb-80ed-9ffe9bf7bff9. Accessed February 27, 2019.

20. Cochrane Skin Group Core Outcome Set Initiative. Project groups. https://www.uniklinikum-dresden.de/de/das-klinikum/universitaetscentren/zegv/cousin/meet-the-teams/project-groups. Accessed February 27, 2019.

21. Kirkham JJ, Gorst S, Altman DG, et al. Core Outcome Set-STAndards for Reporting: the COS-STAR Statement. *PLoS Med*. 2016;13(10):e1002148. doi:10.1371/journal.pmed.1002148

22. Thiboutot DM, Layton AM, Chren MM, Eady EA, Tan J. Assessing effectiveness in acne clinical trials: steps towards a core outcome measure set. *Br J Dermatol*. 2019;181(4):700-706. Epub ahead of print. Review. doi:10.1111/bjd.18011

23. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess*. 1998;2(3):i-iv, 1-88. doi:10.3310/hta2030

24. Fish R. Introduction to consensus meetings. Presented at the COMET (Core Outcome Measures in Effective Trials) UK meeting for ongoing COS developers; January 11, 2018; London, United Kingdom.

25. Schlessinger DI, Iyengar S, Yanes AF, et al. Development of a core outcome set for clinical trials in squamous cell carcinoma: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials*. 2017;18(1):321. doi:10.1186/s13063-017-2069-2

26. Iyengar S, Williamson PR, Schmitt J, et al. Development of a core outcome set for clinical trials in rosacea: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials*. 2016;17(1):429. doi:10.1186/s13063-016-1554-3

27. Schlessinger DI, Iyengar S, Yanes AF, et al. Development of a core outcome set for clinical trials in facial aging: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *Trials*. 2017;18(1):359. doi:10.1186/s13063-017-2104-3

28. Boers M, Kirwan JR, Tugwell P, et al. The OMERACT Handbook. https://omeract.org. Updated January 19, 2018. Accessed February 27, 2019.

29. Young B, Bagley H. Including patients in core outcome set development: issues to consider based on three workshops with around 100 international delegates. *Res Involv Engagem*. 2016;2:25. doi:10.1186/s40900-016-0039-6

30. Tillett W, Eder L, Goel N, et al. Enhanced patient involvement and the need to revise the core set—report from the Psoriatic Arthritis Working Group at OMERACT 2014. *J Rheumatol*. 2015;42(11):2198-2203. doi:10.3899/jrheum.141156

31. Smith H, Horobin A, Fackrell K, Colley V, Thacker B, Hall DA; Core Outcome Measures in Tinnitus (COMiT) initiative. Defining and evaluating novel procedures for involving patients in Core Outcome Set research: creating a meaningful long list of candidate outcome domains. *Res Involv Engagem*. 2018;4:8. doi:10.1186/s40900-018-0091-5

32. Jones JE, Jones LL, Keeley TJH, Calvert MJ, Mathers J. A review of patient and carer participation and the use of qualitative research in the development of core outcome sets. *PLoS One*. 2017;12(3):e0172937. doi:10.1371/journal.pone.0172937

33. Philipp-Dormston WG, Müller K, Novak B, et al; NMSC-QoL Study Group. Patient-reported health outcomes in patients with non-melanoma skin cancer and actinic keratosis: results from a large-scale observational study analysing effects of diagnoses and disease progression. *J Eur Acad Dermatol Venereol*. 2018;32(7):1138-1146. doi:10.1111/jdv.14703

34. Neri L, Peris K, Longo C, et al; Actinic Keratosis - TReatment Adherence INitiative (AK-TRAIN) study group. Physician-patient communication and patient-reported outcomes in the actinic keratosis treatment adherence initiative (AK-TRAIN): a multicenter, prospective, real-life study of treatment satisfaction, quality of life and adherence to topical field-directed therapy for the treatment of actinic keratosis in Italy. *J Eur Acad Dermatol Venereol*. 2019;33(1):93-107. doi:10.1111/jdv.15142

35. Kirby JS, Gregory T, Liu G, Leslie DL, Miller JJ. Variation in the cost of managing actinic keratosis. *JAMA Dermatol*. 2017;153(4):264-269. doi:10.1001/jamadermatol.2016.4733

36. Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. *J Invest Dermatol*. 2012;132(5):1497-1500. doi:10.1038/jid.2011.459

37. Weinstock MA, Thwin SS, Siegel JA, et al; Veterans Affairs Keratinocyte Carcinoma Chemoprevention Trial (VAKCC) Group. Chemoprevention of basal and squamous cell carcinoma with a single course of fluorouracil, 5%, cream: a randomized clinical trial. *JAMA Dermatol*. 2018;154(2):167-174. doi:10.1001/jamadermatol.2017.3631