Development of a core outcome set for basal cell carcinoma

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Background: There is variation in the outcomes reported in clinical studies of basal cell carcinoma. This can prevent effective meta-analyses from answering important clinical questions.

Objective: To identify a recommended minimum set of core outcomes for basal cell carcinoma clinical trials.

Methods: Patient and professional Delphi process to cull a long list, culminating in a consensus meeting. To be provisionally accepted, outcomes needed to be deemed important (score, 7-9, with 9 being the maximum) by 70% of each stakeholder group.

Results: Two hundred thirty-five candidate outcomes identified via a systematic literature review and survey of key stakeholders were reduced to 74 that were rated by 100 health care professionals and patients in 2 Delphi rounds. Twenty-seven outcomes were provisionally accepted. The final core set of 5 agreed-upon outcomes after the consensus meeting included complete response; persistent or serious adverse events; recurrence-free survival; quality of life; and patient satisfaction, including cosmetic outcome.

Limitations: English-speaking patients and professionals rated outcomes extracted from English language studies.

Conclusion: A core outcome set for basal cell carcinoma has been developed. The use of relevant measures may improve the utility of clinical research and the quality of therapeutic guidance available to clinicians. (J Am Acad Dermatol 2022;87:573-81.)

Key words: basal cell carcinoma; core; measure; outcome; set; skin cancer.

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INTRODUCTION

Basal cell carcinoma (BCC) represents over three-quarters of nonmelanoma skin cancers.[1,2] BCCs may cause local tissue destruction, cosmetic disfigurement, and reduced quality of life.[3] Although surgical excision is the first-line treatment, other treatments include electrodesiccation and curettage, topical immunomodulators and chemotherapies, photodynamic therapy, targeted systemic therapies, and radiotherapy.[3,4]

Despite the ubiquity of studies on BCC treatment, the reporting of dissimilar outcomes across studies hinders the pooling of data in systematic reviews, meta-analyses, and treatment guidelines.[3,5] The lack of standardization also increases the risk of selective outcome reporting or results-based selection of outcomes for publication, which may result in inflated effectiveness estimates.[6]

The use of core outcome sets (COSs), minimum sets of agreed-upon outcomes that should be reported in all trials on a given condition or disease state, can facilitate direct comparison of results across studies. Additionally, COSs have the potential to reduce publication bias. Importantly, COSs do not limit the number of reportable outcomes because, in addition to the core set, researchers may report additional outcomes of interest.[7]

In the last decade, COS development has gained momentum in dermatology.[8,9] The purpose of this study was to create a COS for BCC intervention studies.

CAPSULE SUMMARY

- Standardized reported outcomes across a range of disparate clinical studies can facilitate systematic reviews, meta-analyses, and treatment guidelines.
- The consensus panel recommends the following 5 core outcomes to measure basal cell carcinoma treatment response: complete response, recurrence-free survival, persistent or serious adverse events, patient satisfaction, and quality of life.

METHODS

Systematic literature review

In July 2016, a literature search was conducted in PubMed, Embase, and the Cochrane Library for English language human studies published between January 1985 and July 2016. Search terms included "basal cell carcinoma" and "treatment." Title, abstract, and full-text review was performed by 2 reviewers (DS, EP). Included studies were prospective with at least 1 reported clinical outcome.

Outcome extraction and development of the outcome list

All reported outcomes were extracted to create a long list. Then, dermatologists, nurses, physician assistants, medical regulatory personnel, and patients were asked to suggest additional outcomes. Dermatologists were selected from a group that had published on BCC treatment or presented at major national or international meetings during the past 5 years. Nondermatology providers were a convenience sample. Medical regulatory personnel included chairs of institutional review board panels and directors of clinical trials units. All except regulatory personnel and 2 patients were engaged in patient care. Outcomes were collapsed by the steering committee to avoid redundancy and grouped into domains.

Recruitment of Delphi participants

The stakeholder groups recruited for participation in the Delphi were physicians and patients. Patients with a history of BCC treated by a dermatologist were nominated by Measurement of Priority Outcome Variables in Dermatologic Surgery (IMPROVED) members and had different disease extents, including single tumors, multiple tumors over time, BCC syndromes (eg, Gorlin's), and advanced BCC; different sexes; and different ages, from 32 to 91 years. Physicians were US and international dermatologists as well as nondermatology physicians who had published in the past 10 years on BCC and/or presented at major national or international meetings. In addition, physicians were screened for potential conflicts of interest.

Delphi consensus method

From the master lists of physician and patient participants, individuals were randomly invited to participate until a total of 63 physicians and 35 patients agreed, to ensure that at least 20 participants in each category completed the Delphi process.

To achieve group consensus while minimizing bias, candidate outcomes were rated and scored through the web-based eDelphi software (DelphiManager software, version 3.0) as well as Qualtrics software (Qualtrics XM, Qualtrics). Delphi surveys are widely used in health care research and involve iterative scoring by individual participants of the relative importance of each item in a list.[10] Two Delphi rounds were performed. Links to the eDelphi surveys were distributed via email.

Abbreviations used:

BCC: basal cell carcinoma
COS: core outcome set

For each round, each outcome was rated as either "not important" (score, 1-3), "uncertain" (score, 4-6), or "important" (score, 7-9). Stakeholders could also select "unable to score." Lay descriptions of each outcome were provided for patient raters.

Outcomes presented for rating in round 2 included those in round 1 plus new outcomes proposed by stakeholders. Before participants scored outcomes in round 2, they were provided the frequencies and distributions of physician or patient scores from round 1 in a graphical format.

Consensus criteria

To meet the provisional criteria for inclusion, outcomes had to be rated as 'important' by at least 70% of the professional and patient stakeholders. Outcomes rated as 'not important' by at least 70% of both stakeholder groups were excluded. Provisionally included and undecided outcomes were voted upon at consensus meetings.

Consensus meeting

All participants were invited to consensus meetings. Items that had achieved provisional inclusion criteria were discussed and voted on by the participants to be "included" or "not included." Subsequently, the undecided outcomes that were deemed to be of interest were reviewed. Voting continued until consensus was reached regarding the core set. Participants' votes were weighted equally.

Statistical analysis

Descriptive statistics were calculated using SAS Studio version 3.7 (SAS Institute Inc). Percent agreement and mean scores for each outcome were calculated separately for the patient and professional stakeholders.

Guidance for COS development

The development of this COS followed the standards set forth by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative,[11] the Cochrane Skin Group Core Outcomes Set Initiative (CSG-COUSIN),[12] and the Harmonising Outcome Measures for Eczema (HOME) roadmap.[13] The reporting of this COS is in accordance with the Core Outcome Set Standards for Reporting checklist (COS-STAR) developed by Kirkham et al.[14]

COS registration

This COS was registered with both Core Outcome Measures in Effectiveness Trials and Cochrane Skin Group Core Outcomes Set Initiative.[15,16] The study protocol was previously published.[17] The Delphi consensus was approved by the Northwestern University institutional review board (STU00097285).

RESULTS

Literature search and outcome identification

The literature search is summarized in Fig 1.[18] Overall, 235 discrete outcomes were extracted from 70 studies, including 50 nonsurgical studies and 20 surgical interventions. Next, 20 stakeholders, including 14 dermatologists representing 4 countries, 2 primary care physicians, a nurse, a physician assistant, a medical assistant, and an industry scientist, were surveyed for their input regarding additional outcomes that they deemed important. Finally, the list of outcomes was condensed by a steering committee,* with 74† outcomes included in the Delphi. Outcomes were organized into domains: recurrence, progression, and remission (16); clinical assessment (14); safety and tolerability of treatment (10); treatment effectiveness (9); histologic assessment (9); procedural factors (7); pharmacokinetic considerations (5); and patient satisfaction (4).

Delphi participant characteristics

Sixty-five professionals and 35 patients participated in Delphi round 1. Participants' demographic information is summarized in Table I. Professional stakeholders were dermatologic surgeons (54%), general dermatologists (27%), oncologists (10%), and other specialists (10%). Most patients had a master's degree or higher and were predominantly White. Round 2 was completed in June 2021 by 58 professionals (89.2% retention) and 34 patients (97.1%).

*This steering committee of the IMPROVED (Measurement of Priority Outcome Variables in Dermatologic Surgery) group, a multidisciplinary association of physicians and other stakeholders committed to the development of core outcome sets relevant to cutaneous surgery, aesthetic medicine, and skin cancer, is comprised of 4 dermatologic surgeons and skin cancer treatment experts, (MA, TVC, IAM, JFS).

†Seventy-two candidate outcomes were included in round 1, and 2 additional outcomes were proposed by stakeholders in round 1, which resulted in a total of 74 outcomes that were included in round 2.

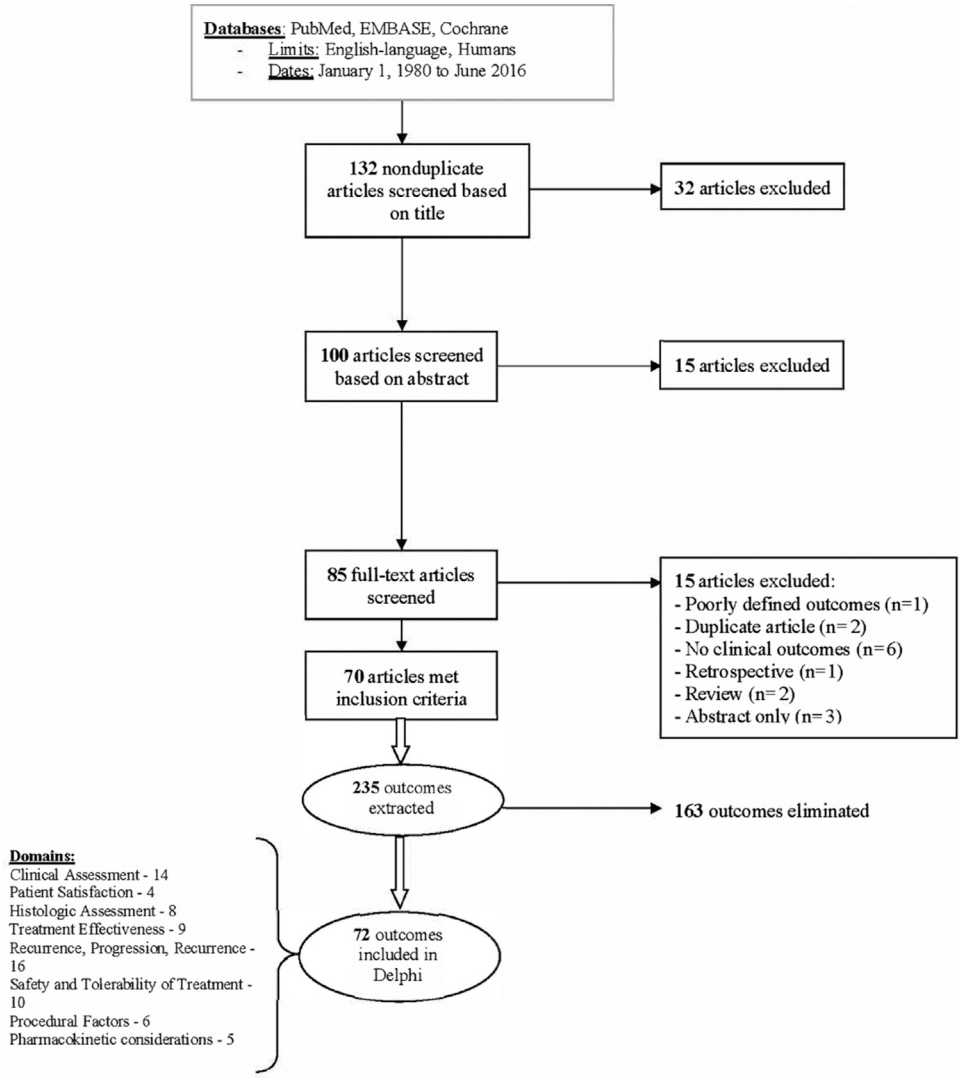

Fig 1. Systematic literature review and identification of candidate outcomes for Delphi surveys.[18]

Delphi results

Delphi results are provided in Supplementary Table I (available via Mendeley at https://data.mendeley.com/datasets/bnn75z6gvr/1). Two additional outcomes were proposed in round 1 and included in round 2. Of the 74 outcomes rated, 27 met the provisional inclusion criteria. These included treatment effectiveness, absence of clinical response, total clearance, treatment failure, disease progression, histologically confirmed tumor recurrence, progression-free survival, recurrence-free survival, allergic reaction, patient satisfaction, and skin-related quality of life. No items were excluded, with the remainder classified as undecided.

Consensus meeting

A consensus meeting convened in July 2021 included international experts in oncology, general dermatology, dermatologic surgery, and COS development. Thirty-four individuals, including 28 physicians (21 dermatologic surgeons, 5 general dermatologists, and 2 other specialists) and 6 patients, participated and an additional 4 sent written comments. Items meeting the provisional inclusion criteria were discussed and voted on anonymously to be either included or not included in the final core set.

Of the 27 outcomes meeting the provisional inclusion criteria, 5 were voted into the final core set. Treatment failure was subsumed under total clearance and was voted out. Treatment effectiveness and disease progression (ie, progression-free survival) were unanimously considered relevant to account for populations and modalities for which total clearance may not be feasible; however, they were deemed to have overlap with tumor clearance (ie, complete response) and recurrence-free

Table I. Demographic characteristics of Delphi survey stakeholders

Demographic features	Participants, No. (%)	
	Round 1	Round 2
Total patients, No. (%)	35	34 (97.1)*
Age (y), mean	59.4	59.75
Sex, No. (%)		
Male	24 (68.6)	24 (70.6)
Female	11 (31.4)	10 (29.4)
Fitzpatrick skin type, No. (%)†		
I	8 (22.9)	7 (20.6)
II	15 (42.9)	15 (44.1)
III	9 (25.7)	9 (26.5)
IV	3 (8.6)	3 (8.8)
Ethnicity, No. (%)†		
Hispanic or Latino	0	0
Not Hispanic or Latino	35 (100)	34 (100)
Education, No. (%)†		
High school diploma	4 (11.4)	4 (11.8)
Bachelor's degree (BA/BS)	9 (25.7)	9 (26.5)
Master's degree	11 (31.4)	10 (29.4)
Doctoral degree	11 (31.4)	11 (32.4)
Total health care professionals, No (%)	65	58 (89.2)*
Total physicians, No. (%)	63	58 (92.1)
Specialty, No. (%)		
General dermatology	17 (27.0)	16 (95.4)
Dermatologic surgery	34 (54.0)	31 (53.4)
Oncology	6 (9.5)	6 (10.3)
Other specialties	6 (9.5)	5 (8.6)
Geographic region, No. (%)		
United States	48 (76.2)	44 (75.9)
Canada	2 (3.2)	2 (3.4)
Europe	13 (20.6)	12 (20.7)

BA, Bachelor of Arts; *BS*, Bachelor of Science.
*Expressed as a percentage of the number of stakeholders who participated in round 1.
†Patient-reported.

survival, respectively. Because most BCCs are curable, not advanced or metastatic, a decision was made to retain complete response and recurrence-free survival while recommending that treatment effectiveness and progression-free survival also be considered in studies of advanced, syndromic, or metastatic BCC. Similarly, although both partial and complete responses were considered relevant, to keep the number of core outcomes feasible and in recognition of the likelihood of achieving a cure for BCC in most cases, only complete response was retained. Recurrence-free survival was deemed to be based on clinical as well as histologic evaluation. Patient satisfaction and quality of life were identified as the 2 most important patient-reported outcomes. Participants discussed the likely influences on quality of life, which they agreed included potential disfigurement, functional disability, and impact on work and social commitments. Although participants agreed that cosmetic outcomes should be evaluated in all BCC clinical trials, they included this as a component of patient satisfaction, leading to the revised outcome, "patient satisfaction, including with cosmetic outcome."

Consensus meeting participants unanimously voted adverse events into the final set. However, because participants were concerned that minor, self-limited, and self-remitting treatment-related effects such as mild edema and erythema not obscure the elicitation of more clinically significant effects, they further refined the adverse event outcome to include only "persistent or serious adverse events."

Final COS

The final core set of 5 agreed-upon outcomes included complete response; persistent or serious adverse events; recurrence-free survival; quality of life; and patient satisfaction, including cosmetic outcome. The operational definitions of each of these outcomes are provided in Table II.

DISCUSSION

This set of 5 core outcomes for BCC was established on the basis of the consensus of patients and an international group of dermatologists. At a minimum, we recommend that all BCC trials should report these core outcomes. The implementation of this COS by researchers will help facilitate the comparison of results across trials. Conversely, failure to report these outcomes may result in the overlook of an aspect of BCC treatment that has been deemed important by both patients and physicians.

The results of this Delphi process are consistent with much of the BCC literature. The recent guidelines set forth by the American Academy of Dermatology on BCC management acknowledge that recurrence rate, patient expectations, and adverse events are important considerations in choosing an appropriate treatment strategy.[19] In addition, a systematic review and network meta-analysis by Drucker et al[3] recommended that all trials report lesion recurrence, adverse events, and cosmetic outcomes.

Tumor clearance and tumor recurrence have been frequently reported as primary outcomes in BCC trials. Although recurrence-free survival was included in the final core set, no consensus was reached regarding the length of follow-up. Given that two-thirds of recurrences appear in the 3 years after treatment, follow-up for 36 months has been previously recommended,[5] although admittedly, this may be impractical in some studies. Cosmetic

Table II. Final core outcome sets for basal cell carcinoma*

Outcome	Core outcome set	Additional outcomes to be considered in studies of very aggressive tumors‡	Definition
Complete response	X		The absence of all signs of tumor after treatment.
Partial response		X	A decrease in the size of the tumor after treatment but some tumor remains.
Recurrence-free survival	X		The length of time after the initial treatment during which a patient has no signs or symptoms of cancer. Also referred to as disease-free survival or relapse-free survival; this refers to the durability of a complete response.
Progression-free survival		X	How long after treatment a patient's cancer does not get worse or grow.
Persistent or serious adverse events	X		The frequency and severity of any side effects of treatment that are persistent (as versus short-term and self-remitting) or serious† including both local and systemic symptoms.
Patient satisfaction, including cosmetic outcome	X		The degree to which patients are pleased with the overall course of treatment, including the appearance of the treatment site and adjacent structures.
Quality of life (global)	X		Patients' report of their general well-being.

*Outcomes were included in the final core outcome set if at least 50% of consensus meeting participants voted in favor. In some cases, 2 or more selected outcomes that were deemed essential at the consensus meeting were combined or coalesced into a single core outcome.
†Per US Food and Drug Administration guidelines: death; life-threatening outcomes; hospitalization; disability or permanent damage; congenital anomaly/birth defect; required intervention to prevent permanent impairment or damage; and other serious or important medical events that may jeopardize the patient and require medical or surgical intervention to prevent one of other serious adverse events.
‡Very aggressive tumors are those with high risk of recurrence; extensive soft tissue invasion, bone invasion, or invasion of critical structures (eg, periorbital region or eye); or those that are potentially life-threatening including with regional or distant metastasis.

outcomes have also commonly been reported as primary or secondary outcomes, although many of the multitudes of scales for this purpose are insufficiently validated.[20] Patient-reported outcomes such as quality of life and satisfaction with treatment have been less consistently reported. However, given that BCC is rarely fatal but often troublesome, painful, expensive, disruptive, and anxiety-provoking patient-reported outcomes are particularly relevant.[21] Regarding adverse events, consensus meeting participants felt that the frequency and severity of adverse events, particularly when these were persistent and serious, must be reported to enable the comparison of safety profiles across different treatment modalities.

Consensus meeting participants did note that although most BCCs are curable, a small minority of the most troublesome and threatening tumors are syndromic, advanced, or metastatic. For intervention studies of these highly aggressive and treatment-resistant tumors, the core outcomes of complete response and recurrence-free survival may not be sufficiently sensitive and nuanced. Therefore, in studies of such highly aggressive tumors, it may be appropriate to measure additional non-core outcomes, such as treatment effectiveness or partial response and progression-free survival.

Several outcomes were excluded because of the disparate perception of their importance among patients and professionals. For instance, Mohs defect size, medication adherence, and cost effectiveness were more important to physicians than patients. The reasons for these differences and other similar differences are unclear and may be useful to investigate further. It is possible that patients may care more about cure and ultimate cosmesis, which are later stage outcomes that they know and understand. Patients may be more accepting of cost, inconvenience, and large wounds as necessary correlates of cancer treatment.

None of the outcomes in the Delphi were removed on the basis of preset exclusion criteria. This may be because of the previously described "ceiling effect" observed with Likert scale–based scoring, where results are skewed in favor of higher responses.[22,23] Future COS methodology groups may consider limiting the number of

important ratings per participant or mandate rank-ordering of choices to yield more discriminant Delphi results.

The development of this COS was inclusive, with a range of stakeholders with diverse expertise from several countries and with validation by both patients and professionals. Further, this COS was developed for use with both surgical and nonsurgical treatment modalities. Although a limitation of our study is that dermatologists and dermatologic surgeons comprised the majority of respondents and although this could introduce unintentional bias, we did include several other specialists (Table I) who were also able to vote in the Delphi process. Moreover, the vast majority, probably 99% or more, of BCCs are treated exclusively by dermatologists and dermatologic surgeons.

A limitation was that only English-speaking patients and professionals rated outcomes extracted from English language studies. In addition, although a more diverse patient representation would have been preferred, the enrollment of mostly White patients may be reflective of the increased likelihood of BCC in patients with fairer skin. Finally, this study would have benefited from additional patient input at the consensus meeting. Another limitation is that the literature search that initiated the development of this COS was performed 6 years ago. However, given that the search was only intended to elicit the types of outcomes that have been measured rather than the specific values of such outcomes, it is unlikely, although possible, that a more recent literature search would have detected outcomes not previously measured by any investigators. Finally, we would expect that had such additional outcomes emerged during the preceding 6 years, these would have been identified by the many stakeholders consulted, or added by patients or physicians in the multiple recent Delphi rounds designed to arrive at a COS.

Per standard COS methodology, the first step in the process of outcome consensus in establishing what should be measured, followed by standardization of how those outcomes should be measured.[11-13] Therefore, the next step would be to systematically review the various measures available for assessing the remaining core outcomes in this set in order to select associated core outcome measures via a similar consensus-driven process.

Conflicts of interest

Dr Kirkham is involved with the COMET and CS-COUSIN Methods groups. Drs Schmitt and Alam are involved with the CS-COUSIN Methods group. Dr Armstrong has served as a research investigator and/or scientific advisor to AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, Pfizer, and Modmed. The remaining authors have no relevant conflicts to disclose.

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