




Identification and content validation of wound therapy clinical endpoints relevant to clinical practice and patient values for FDA approval. Part 1. Survey of the wound care community

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ABSTRACT

Wounds that exhibit delayed healing add extraordinary clinical, economic, and personal burdens to patients, as well as to increasing financial costs to health systems. New interventions designed to ease such burdens for patients with cancer, renal, or ophthalmologic conditions are often cleared for approval by the U.S. Food and Drug Administration (FDA) using multiple endpoints but the requirement of complete healing as a primary endpoint for wound products impedes FDA clearance of interventions that can provide other clinical or patient-centered benefits for persons with wounds. A multidisciplinary group of wound experts undertook an initiative, in collaboration with the FDA, to identify and content validate supporting FDA criteria for qualifying wound endpoints relevant to clinical practice (CP) and patient-centered outcomes (PCO) as primary outcomes in clinical trials. As part of the initiative, a research study was conducted involving 628 multidisciplinary expert wound clinicians and researchers from 4 different groups: the interdisciplinary core advisory team; attendees of the Spring 2015 *Symposium on Advanced Wound Care (SAWC)*; clinicians employed by a national network of specialty clinics focused on comprehensive wound care; and Association for the Advancement of Wound Care (AAWC) and Wound Healing Society (WHS) members who had not previously completed the survey. The online survey assessed 28 literature-based wound care endpoints for their relevance and importance to clinical practice and clinical research. Fifteen of the endpoints were evaluated for their relevance to improving quality of life. Twenty-two endpoints had content validity indexes

AAWC	Association for the Advancement of Wound Care	MR	More research
COA	Clinical outcomes assessment	MS	Measures of success
CP	Clinical practice	OR	Odds ratio
CV	Content validity	PCO	Patient-centered outcome
CVI	Content Validity Index	PP	Private practice
EL	Evidence level	R	Relevance
FDA	U.S. Food and Drug Administration	RCT	Randomized controlled trial
HHC	Home health care	UC	University/college
ICAT	Inaugural Clinical Advisory Team	WCC	Wound care center
ICWHWG	Inter-Center Wound Healing Working Group	WEF-CEP	Wound-care Experts/FDA-Clinical Endpoints Project
LTC	Long-term care	WHS	Wound Healing Society

(CVI) ≥ 0.75 , and 15 were selected as meriting potential inclusion as additional endpoints for FDA approval of future wound care interventions. This study represents an important first step in identifying and validating new measurable wound care endpoints for clinical research and practice and for regulatory evaluation.

The clinical, economic, and patient morbidity and mortality burden of chronic wounds exceeds that of several major forms of cancer.¹⁻⁵ While numerous devices, tissues, and a few biologics and drugs have been approved by the United States Food and Drug Administration (FDA) for clinical use, in those instances in which clinical research trials were required for the approval process, the primary efficacy or safety endpoint of complete wound healing was always compulsory. Clinicians who care for patients with chronic wounds recognize that complete healing may not be reasonably expected for many, with similarities to oncology in which efficacious anti-cancer interventions may reduce tumor size but not lead to cure in all instances. Regulatory agencies, including FDA, accept a variety of surrogate outcomes for approval of products for oncologic, ophthalmic, or renal conditions. However, according to the *2006 FDA Guidance For Industry: Chronic Cutaneous Wounds and Burns—Developing Products for Treatment*, new therapies that reduce similar burdens for patients with wounds are approved for use only if they support complete healing, facilitate surgical wound closure, or improve cosmesis and function of healing.⁶ This policy is considered by many wound clinicians and investigators to be out of date because many outcomes besides full wound closure (epithelialization) are clinically meaningful and provide patient benefits.^{2,7}

Wound closure is not always an appropriate or even an achievable outcome for patients with chronic wounds. Depending on patient variables, setting, and timing, many wound outcomes are more important than complete healing;⁸ for example, limb preservation by conducting interventions that avert the need for a major lower extremity amputation can significantly improve patient quality of life, morbidity, and mortality.^{9,10} Since 2006, however, the demand by FDA guidance for complete wound closure has biased clinical trial design and led investigators to overlook other clinically relevant healing precursors and outcomes that are of significance to patients, clinicians, health systems, and payers, as well as to the industry.

Recognizing this discrepancy between clinical needs and regulatory policy, the FDA in 2014 organized the Inter-Center Wound Healing Working Group (ICWHWG) to address agency-wide wound-related issues and to update and improve their guidance documents, including the 2006 FDA Guidance document⁶ for developing chronic wound and burn treatments. The Association for the Advancement of Wound Care (AAWC) offered to assist the FDA group by identifying: (1) key experts on wound care science, clinical care, and clinical research, including clinical trials; and (2) wound endpoints in addition to complete epithelialization that reflect meaningful clinical benefit or patient-centered outcomes. This led to the organization of the Wound-care Experts/FDA-Clinical Endpoints Project (WEF-CEP) whose purpose is to provide meaningful data

and interpretation of endpoints to help the FDA group revise the 2006 Guidance document. The objectives of this first phase of the project were to (1) identify scientifically achievable, clinically relevant, and patient-centered wound endpoints supporting their capacity to serve as primary wound care outcomes; and (2) determine the content validity of the endpoints by surveying the wound care community. This report describes the findings and interpretations supplied to the FDA group.

METHODS

A survey was designed for clinicians engaged in real world wound care practice to collect data on clinical outcome assessments (COAs) and other assessments as an alternative to complete wound closure, and especially step 2 of the FDA's Roadmap to Patient-Focused Outcome Measurement in Clinical Trials, part of the Clinical Outcome Assessment Qualification Program.¹¹ The 3 steps of the roadmap include (1) understanding the disease or condition; (2) conceptualizing treatment benefit, which involves identifying the concept of interest for meaningful treatment benefit, defining the context of use, and selecting the type of COA; and (3) selecting/developing the outcome measure, which means COA development by measuring the concept of interest in the context of use. To support a COA qualification, content validity evidence must be adequate, instrument reliability and cross-sectional evaluation of construct validity has to be determined, and finally longitudinal evaluation must be undertaken. A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm (our survey included some of these), COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer.¹² Table 1 details the 4 possible COAs while Table 2 explains these concepts in more detail using patient-reported outcome instruments as an example. In this paper, we will focus primarily on content validity.

Clinical outcome assessments measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. They can be employed in well-conducted randomized controlled trials (RCT) to determine whether or not an agent has been demonstrated treatment benefit, in which benefit is defined in terms of safety and efficacy compared with other treatments in the same conditions of use. In contrast to clinical outcomes, clinical endpoints are clearly documented measurements used to determine impact of an intervention on a recognized clinical, patient-based, or economic outcome. Defining the endpoint starts with identifying a particular method for patient assessments obtained at one or more

Table 1. The 4 types of clinical outcome assessments (COAs)

COA	
Clinician-reported outcome (ClinRO)	<ul style="list-style-type: none"> • Based on a report that comes from a trained healthcare professional after observation of a patient's health condition. • Measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. • Measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity).
Observer-reported outcome (ObsRO)	<ul style="list-style-type: none"> • Measurement based on an observation by someone other than the patient or a health professional (e.g., parent, spouse, or other nonclinical caregiver who can regularly observe and report on a specific aspect of the patient's health). • Measure does not include medical judgment or interpretation.
Patient-reported outcome (PRO)	<ul style="list-style-type: none"> • Measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else. • Can be measured by self-report or by interview, provided that the interviewer records only the patient's response. • Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. • Can also assess the patient perspective on functioning or activities that may also be observable by others.
Performance outcome (PerFO)	<ul style="list-style-type: none"> • Measurement based on a task(s) performed by a patient according to instructions that is administered by a healthcare professional. • Performance outcomes require patient cooperation and motivation (e.g., timed 25 foot walk test, memory recall, or other cognitive testing).

Source: Adapted from FDA web page.¹²

specified times during the clinical study, constructing the related endpoint, and specifying a statistical method to be used for conducting analysis to compare effects between groups.¹⁴ *In general, the assessment itself, in isolation from the other specified endpoint elements, is not usually the endpoint, although in wound care they may occasionally be the same.* This is important to recognize because other aspects of an endpoint, e.g., number of evaluations, study time points and statistical methods, will also affect interpretation of the study results.¹⁵

An important aspect of any endpoint is its content validity (CV), which can be defined as the extent to which the elements within a measurement procedure are relevant and representative of the construct that they will be used to measure.¹⁵ In ordinary language, when applied to an endpoint, the endpoint must be appropriate to the wound care population for which it is intended (i.e., must be applicable to all of the targeted population) and measure a relevant concept in such a way that the data can be meaningfully and ultimately comprehensively analyzed in regard to the intervention being tested when the study is of therapeutic design.

Survey development

From October 2014 to December 2014 our core group developed a proof-of-concept (POC) survey to validate the

relevance of selected outcomes published in the wound care literature in regard to clinical practice (CP) and patient-centered outcomes (PCO). In step 1 a comprehensive list of these outcomes or endpoints was identified. This list of 28 wound healing endpoints was developed to include those that have previously been submitted to the FDA for wound products under investigation, and other endpoints and outcomes deemed important based on experience from clinical practice and from conducting clinical trials.

A final survey instrument was developed based on the 28 endpoints. To establish each endpoint's content validity, relevance (R) to clinical practice was rated using a 4-point Likert scale (1 = not relevant; 2 = slightly relevant; 3 = moderately relevant; 4 = highly relevant). Perceived adequacy of the level of evidence (EL) supporting each endpoint was rated similarly (1 = none; 2 = very little; 3 = adequate; 4 = ample). A truncated set of 15 endpoints determined to be most meaningful to patient values, compared with relevance to clinical decision making, was also created with each endpoint rated on a 4-point scale (1 = no difference; 2 = slight difference; 3 = moderate difference; 4 = significant difference). In addition, respondents were asked for their expert opinion on whether all endpoints need more research (MR) before recommending to the FDA. Out of the 28 endpoints, respondents were allowed to select a maximum of 5 endpoints for which to answer

Table 2. Measurement properties considered in the review of PRO instruments used in clinical trials

Measurement property	Type	What is assessed?	FDA review consideration
Reliability	Test–retest or intra-interviewer reliability (for interviewer-administered PROs only)	Stability of scores over time when no change is expected in the concept of interest	<ul style="list-style-type: none"> • Intraclass correlation coefficient • Time period of assessment
	Internal consistency	<ul style="list-style-type: none"> • Extent to which items comprising a scale measure the same concept • Intercorrelation of items that contribute to a score • Internal consistency 	<ul style="list-style-type: none"> • Cronbach’s alpha for summary scores • Item-total correlations
	Inter-interviewer reliability (for interviewer-administered PROs only)	Agreement among responses when the PRO is administered by two or more different interviewers	<ul style="list-style-type: none"> • Interclass correlation coefficient
Validity	Content validity	Evidence that the instrument measures the concept of interest including evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity.	<ul style="list-style-type: none"> • Derivation of all items • Qualitative interview schedule • Interview or focus group transcripts • Items derived from the transcripts • Composition of patients used to develop content • Cognitive interview transcripts to evaluate patient understanding
	Construct validity	Evidence that relationships among items, domains, and concepts conform to <i>a priori</i> hypotheses concerning logical relationships that should exist with measures of related concepts or scores produced in similar or diverse patient groups	<ul style="list-style-type: none"> • Strength of correlation testing a priori hypotheses (discriminant and convergent validity) • Degree to which the PRO instrument can distinguish among groups hypothesized a priori to be different (known groups validity)
Ability to detect change		Evidence that a PRO instrument can identify differences in scores over time in individuals or groups (similar to those in the clinical trials) who have changed with respect to the measurement concept	<ul style="list-style-type: none"> • Within person change over time • Effect size statistic

Source: Adapted from FDA document.¹³

yes that they needed more research. Finally, respondents were asked whether all endpoints were suitable measures of success (MS) for new drugs, products, or procedures. Respondents were allowed to select a maximum of 10

endpoints for which to answer “yes” out of the possible 28 endpoints.

Additional data collected from the survey included professional category (choice of 22 categories or “other,” in

which respondents were asked to fill in their category; certification(s); and setting(s) in which the respondent practiced. The core team also conducted a pilot test of the survey to evaluate if it clearly communicated the wound endpoint descriptions before the broader wound care community was surveyed. No changes were recommended.

Survey administration

From January 2015 through September 2015, the WEF-CEP issued four separate invitations to interdisciplinary professionals and educators engaged in wound care across United States settings to participate in the WEF-CEP survey. Individuals were asked not to repeat the survey. The online survey was created using *SurveyMonkey* (SurveyMonkey, Palo Alto, CA).

Survey 1, (January–March, 2015) elicited responses from an interdisciplinary Core Advisory Team; Survey 2 elicited responses from combined AAWC and WHS members and attendees of the Spring 2015 *Symposium on Advanced Wound Care (SAWC)* April 29–May 3, 2015 in San Antonio, Texas; Survey 3, (August–September, 2015) elicited responses from a sample of clinicians employed by a national network of specialty clinics focused on comprehensive wound care; and Survey 4 (September–October, 2015) elicited responses from all AAWC and WHS members who had not previously completed the survey and other similar individuals preregistered for the SAWC meeting Fall 2015.

Survey statistical analysis

Because the survey was administered at four different times a variable termed *survey* with values of 1–4 was created. Two complementary variables termed *medical specialty* and *nonmedical specialty* were created with values for the first variable of general surgery, internal medicine/family practice, plastic surgery, podiatry/podiatric surgery, cardiology/vascular medicine/surgery, and other; and registered nurse, nurse practitioner, physical therapist, advanced practice nurse, researcher, and other for the second variable. A collapsed variable based on these variables termed *specialty* comprised 2 values: medical and nonmedical specialty. All wound care certifications were reduced to a binary variable termed *wound care certified*. Work settings were not mutually exclusive. Consequently, a series of binary variables were used to describe the setting in which respondents were employed: system (Veterans Administration, US military, hospital), corporate/industry/research; noncorporate research, UC (university/college); WCC (wound care clinic); PP (private practice); HHC (home healthcare); LTC (long-term care); and other.

Categories were analyzed by count and percentage of respondents. Four-point (1–4) responses were assigned the appropriate numerical values. Missing values (blank field) were imputed for

EL endpoint responses of “I am not sure” (an additional allowed response for EL endpoint responses) and in any case in which a response was absent. Means and standard deviations were determined for CP, EL, and PCO assessment of endpoints while counts and percentage of respondents responding “yes” were determined for MR and MS endpoints. Spearman’s rho statistic was used to calculate

correlations between participants’ responses for CP, PCO, and EL endpoints. Kendall’s tau b was used to analyze the correlations between ranked CP, EL, and PCO endpoints versus the ranking of the MR endpoints; a similar analysis was conducted between ranked CP, EL, and PCO endpoints versus ranked MS endpoints.

For each of the CP, PCO, and EL endpoints, ordinal logistic regression was conducted to determine how ratings (the dependent variable) were influenced by demographic factors (survey, specialty, wound care certified, and the setting variables). Only models with any statistically significant levels of these factors were refined. Refined model checks included goodness of fit (Pearson or deviance) and the parallel lines test (null hypothesis vs. general model). Further model refinement was not pursued as it was not the purpose of this research to perfect models for predictive or screening validity in clinical use. Statistical significance was set at $p \leq 0.001$ to highlight the most important results.

Content validity

For each of the 28 endpoints listed in the survey, per FDA criteria for qualifying a new clinical outcome assessment, content validity was calculated using judgment quantification, according to established methods^{16,17} based on each respondent’s ratings of CP and of PCO. The content validity index (CVI) for CP of each endpoint was calculated as the number of respondents in all four surveys rating that endpoint moderately or highly on CP (3 or 4) divided by the total number of respondents in all four surveys rating CP of the same endpoint a 1, 2, 3, or 4. This CVI represents the proportion of those rating the individual endpoint “moderately” or “highly” relevant for use in clinical practice. A similar PCO CVI was calculated as the percentage of respondents rating each PCO endpoint “moderately” or “highly” relevant for patients’ lives. Recommendations with a CVI of at least 0.75 were considered “content validated,” reflecting a consolidated opinion of interdisciplinary wound care respondents to the survey that the endpoint was perceived as relevant in supporting clinical practice (CP) or relevant to patients’ lives (PCO). Content validity was not calculated for perceived EL, which is not involved in qualifying an endpoint as a new clinical outcome assessment.

Endpoint CP ratings were correlated with corresponding PCO ratings within and across surveys and specialties using Kendall’s tau b, a nonparametric correlation for the discrete four-point scale used to rate the endpoints. For example, correlating CP and PCO ratings of an endpoint, a high positive Kendall’s tau b, nearly at its maximum value of 1.0 would reflect that survey respondents agreed strongly in their CP and PCO ratings of that endpoint, believing it important to both clinicians and patients. In contrast, a low negative Kendall’s tau b value approaching its minimum of -1.0 would indicate that those who rated the endpoint high on clinical practice relevance also rated it low as a patient-centered outcome relevant to patients’ lives.

A Kendall’s tau b of at least 0.7 represents a very strong relationship; 0.4–0.699, a strong relationship; 0.3–0.399, a moderate relationship, 0.2–0.299 a weak relationship; and 0–0.199 implies that the variables are likely unrelated, even if significant p values are encountered.

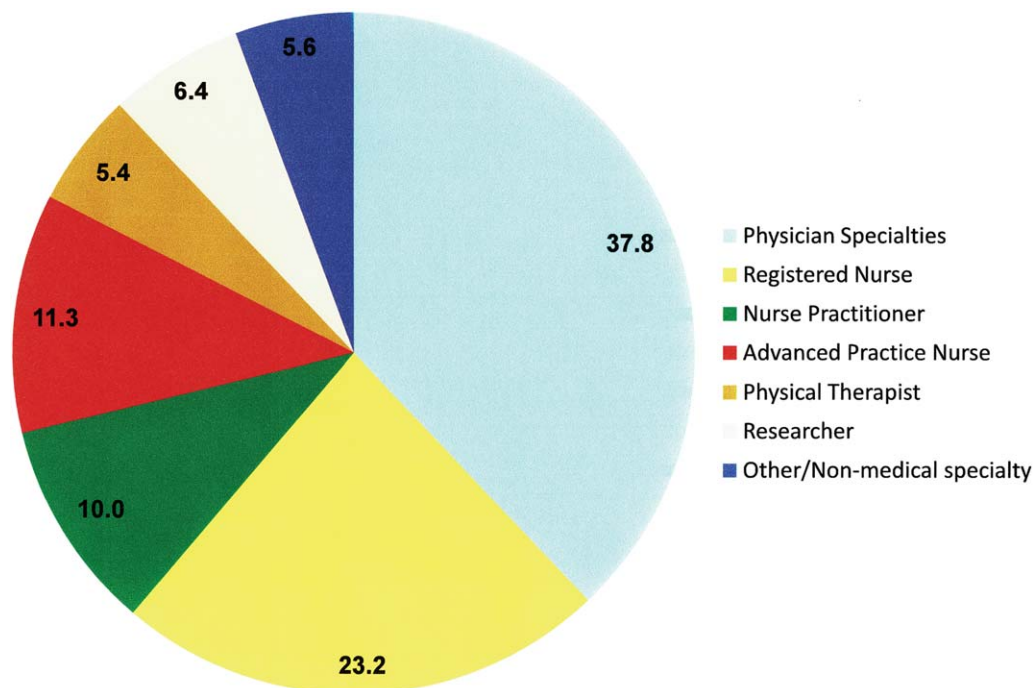


Figure 1. Professional profile of the WEF-CEP survey respondents who reported their specialties. [Color figure can be viewed at wileyonlinelibrary.com]

RESULTS

Demographics

During 2015, 628 unique participants completed the demographics section of the WEF-CEP Survey. Overall in all four surveys, physicians collectively represented the largest proportion of respondents (37.8%), followed by registered nurses (23.2%), “other” medical specialists (18.9%), physical therapists (11.5%), and nurse practitioners (10%) (Figure 1).

Survey 1 respondents (n = 58) were core advisory expert wound care specialists consisting of 34.5% physicians (medical doctors of various specialties, doctor of osteopathy, or doctor of podiatric medicine) and 65.5% non-physician practitioners (nurse practitioner, physician assistant, clinical nurse specialists, nursing professional, or physical therapist). Survey 2 respondents (n = 271) comprised 41% physicians and 59% nonphysician practitioners compared with Survey 3 respondents (n = 43) who comprised 83.7% physicians and 16.3% nonphysician practitioners. The 256 Survey 4 respondents had fewer physicians (27.9%) and more nonphysician practitioners (72.1%). Overall, 390 (62.1%) were from nonphysician specialties and 238 (37.9%) were physicians.

Many respondents reported working in multiple clinical or academic settings. Most reported practicing in wound care centers (42.7%), acute care systems such as the Veterans Administration, US Military, or civilian hospital settings (37.7%), private practice (14.5%), or long term care (10.2%), with 9.2% in university or college settings, 8.5% in corporate or 4.9% in noncorporate research, 3.8% in home healthcare and 9.6% in “other” settings.

Mean scores and content validity

Of the survey respondents, 91.9% completed the CP endpoint section and 82.3% completed PCO endpoint section. Content validity and mean ratings of both these types of endpoints showed considerable variation (Table 3). The top five highest mean ratings (mean \pm standard deviation) for CP were: *Pain reduction* (3.81 ± 0.48), *infection reduction* (3.79 ± 0.49), *increased physical function and ambulation* (3.78 ± 0.49), *amputation reduction* (3.67 ± 0.69), and *wound bed preparation* (3.66 ± 0.63). Mean relevance ratings for the highest-rated PCO endpoints paralleled those of the three highest-rated CP endpoints. The fourth highest-rated PCO endpoint, *time to heal*, had a mean rating of 3.76 ± 0.54 followed by *amputation reduction* (3.67 ± 0.69), which was ranked fourth for CP.

Content validity indexes for relevance of the PCO subset endpoints closely matched those of the same endpoints for CP, reflecting the high value raters placed on patient benefit. All fifteen PCO endpoints in the combined surveys were content validated ($CVI \geq 0.75$) except *reduced time to re-harvest*. Among the endpoints rated for CP relevance, all were content validated except *time to graft or flap*, *reduced time to re-harvest*, *facilitates wound closure*, *biomarkers*, *reduced scar*, and *time to next therapy*.

Based on ranking of these results and further deliberation by the core team concerning which were the most clinical meaningful and could be measured with validated tools or criteria, 15 endpoints were selected as the highest priority for exploration in the research phase of the project for evidence supporting FDA acceptability for use as clinical outcomes assessments.

Table 3. Content validity and mean relevance ratings for CP and PCO endpoints

Endpoint	Content validity index (PCO)	Content validity index (CP)	Mean rating (PCO)	Mean rating (CP)
Healing				
<i>% Area reduction in 4–8 weeks</i>	NR	0.89	NR	3.49
<i>% Volume reduced by study end</i>	NR	0.85	NR	3.39
<i>Time to heal (PCO)</i>	0.96	0.91	3.76	3.59
<i>Reduced recurrence</i>	NR	0.93	NR	3.59
Increased tensile strength	NR	0.81	NR	3.19
Time to graft or flap (PCO)	0.79	0.67	3.17	2.85
Facilitates wound closure	NR	0.65	NR	2.82
Biomarkers	NR	0.62	NR	2.75
Reduced time to re-harvest (PCO)	0.63	0.36	2.78	2.12
Precedents of healing				
Wound bed preparation	NR	0.94	NR	3.66
Improved perfusion	NR	0.95	NR	3.65
Reduced edema (PCO)	0.92	0.94	3.40	3.60
Reduced % wound necrotic tissue	NR	0.92	NR	3.56
Complications				
<i>Infection reduction (PCO)</i>	0.98	0.98	3.71	3.79
<i>Reduced bioburden</i>	NR	0.91	NR	3.54
Reduced antibiotic use (PCO)	0.87	0.88	3.26	3.39
<i>Amputation reduction (PCO)</i>	0.98	0.92	3.84	3.67
<i>Pain reduction (PCO)</i>	0.96	0.97	3.75	3.81
<i>Reduced analgesic use (PCO)</i>	0.91	0.92	3.48	3.49
<i>Odor reduction (PCO)</i>	0.88	0.91	3.45	3.48
<i>Reduced social isolation (PCO)</i>	0.94	0.90	3.62	3.49
<i>Reduced depression (PCO)</i>	0.91	0.89	3.53	3.49
Reduced Scar (PCO)	0.80	0.71	3.17	2.97
Function				
<i>Increased physical function or ambulation (PCO)</i>	0.99	0.98	3.78	3.78
Cost				
<i>Cost effectiveness</i>	NR	0.89	NR	3.41
<i>Reduced cost of treatment (PCO)</i>	0.89	0.93	3.47	3.54
CE ulcer-free days)	NR	0.76	NR	3.14
Time to next therapy	NR	0.74	NR	2.98

Italicized data indicate endpoints with the highest CP and/or PCO mean relevance ratings selected for further research. NR, not reported.

In regard to the perceived level of evidence, response rates for endpoints varied from a low of 54.7% to a high of 82.8%. Only 5 endpoints had mean scores of 3 or above (3 = adequate): *percentage area reduction at 4, 6, or 8 weeks*, *infection reduction*, *amputation reduction*, *wound bed preparation*, and *perfusion* (Table 4).

Many respondents to the MS (measures of success) endpoints believed that *time to heal* (61.2%), *percent area reduction at 4, 6, or 8 weeks* (59.6%), *percent volume reduction at study endpoints* (54.9%), *infection reduction* (50.4%), or *amputation reduction* (46.4%), would be useful as measures of success in evaluating efficacy of new

drugs, devices, products or procedures. However, the same respondents also thought that *time to heal* (28.4%), *cost-effectiveness* (27.3%), *wound recurrence* (24.7%), and *percent area reduction at 4, 6, or 8 weeks* (23.0%) may need further research before presenting to the FDA (these were the top 4 endpoints).

Correlations between endpoints

Most correlations relating the endpoints' relevance to clinical practice (CP), patient-centered outcomes (PCO), and perceived evidence level (EL) were statistically significant

Table 4. Ranked mean score and standard deviation (SD) of the perceived evidence level associated with the 28 endpoints rated by survey respondents

Endpoint	Mean score	SD
Percent area reduction at 4, 6, or 8 weeks	3.14	0.680
Infection reduction	3.07	0.789
Amputation reduction	3.04	0.783
Wound bed preparation	3.02	0.844
Perfusion	3.01	0.855
Percent reduction of necrotic material	2.96	0.854
Percent volume reduction at study endpoints	2.95	0.710
Edema	2.91	0.850
Time to heal	2.90	0.788
Reduction of bioburden	2.87	0.803
Pain reduction	2.80	0.862
Reduction in antibiotics	2.71	0.805
Increased physical function and ambulation	2.68	0.888
Cost-effectiveness	2.64	0.862
Reduction of analgesics	2.63	0.864
Wound recurrence	2.60	0.889
Reduction in cost of treatment	2.58	0.894
Odor reduction	2.58	0.853
Facilitation of wound closure	2.57	0.700
Time to flap or graft	2.55	0.721
Time to next therapy	2.47	0.843
Reduction in scar	2.47	0.834
Cost-effectiveness (ulcer-free days)	2.46	0.929
Reduction in time to re-harvest	2.43	0.812
Increase in wound tensile strength	2.41	0.873
Reduction in social isolation	2.37	0.904
Biomarkers	2.36	0.873
Reduction in depression	2.33	0.917

due to the large sample of respondents: 333–577 respondents rated any given endpoint's perceived relevance to CP or PCO, and estimated adequacy of supporting evidence level. The only non-statistically significant values of Kendall's tau b were for the correlations between perceived clinical relevance or usefulness and estimated adequacy of supporting evidence for the endpoints *reduced cost of treatment* (0.071) and *increased physical function and ambulation* (0.056). All correlations were positive, indicating that raters generally perceived each endpoint's clinical relevance, capacity to make a difference in patients' lives, and adequacy of the supporting evidence as positively related.

The strongest correlations between relevance of CP and PCO (Kendall's tau $b > 0.400$) were for *reduction in*

depression (0.49), *odor reduction* (0.47), *reduction in scar* (0.47), *reduction in antibiotics* (0.47), *pain reduction* (0.46), *reduced edema* (0.45), and *reduction in social isolation* (0.44). *Reduction in analgesic use* (0.39) was the only other endpoint that approached a strong correlation between ratings of relevance of CP and PCO.

Relevance to clinical practice was only marginally correlated with perceived EL ratings by respondents with Kendall's tau b values ranging from 0.06 (likely unrelated) for *increased physical function and ambulation* to 0.31 (moderate) for *reduction in scar*. Though most correlations were statistically significant due to the large sample size of respondents, the only moderately strong relationships using the Kendall's tau b statistic to test the relationship between relevance to CP and perceived EL were for *reduction in scar* (0.31), *odor reduction* (0.31), and *reduction in bioburden* (0.31). Perceived relevance to clinical practice was moderately associated with the belief that the endpoint was supported by adequate evidence only for these 3 endpoints.

Ordinal logistic regression models of variables affecting ratings

In regard to demographic factors, identity of respondents (i.e., which survey) and respondent setting mattered the most: high-level experts from survey 1 and wound care center respondents, significantly affected respondents' likelihood of rating an endpoint on relevancy to clinical practice or perception of evidence level but not patient-centered outcomes (Table 5). Higher odds ratios (OR) above 1.00 indicate that demographic factors increase the likelihood of a higher rating while lower ORs (<1.00) are associated with the likelihood of a lower rating. Adequacy of the model in terms of fit or assumptions is indicated in the last column as yes/no. *No* indicates that while the effect is significant the structure of the model is deficient and the values of the OR are likely to have additional error.

In regard to CP endpoints, setting was the most common influential factor although for each affected endpoint the type of setting most affecting the results was different. Respondents from the employment settings of wound care centers or a system were more likely to judge CP endpoints as being more relevant, while research respondents judged the *reduction of bioburden* endpoint as being less relevant (Table 5). Wound care-certified respondents also judged *reduction in antibiotics use* and *wound bed preparation* endpoints as being more relevant. However, physician respondents were half as likely to rate *percentage reduction in necrotic material* as being relevant.

In terms of rating the perceived evidence level of endpoints, the high-level experts in Survey 1 were more likely to give high ratings to *facilitating wound closure*, *time to next therapy*, *reduced antibiotic use*, or *perfusion* compared with other groups of respondents, while *wound bed preparation* and *edema reduction* endpoints were more likely to receive higher ratings from wound care center respondents. Finally, cost effectiveness was more likely to receive a higher rating of evidence level from wound care-certified respondents.

Table 5. Strong demographic effects ($p > 0.001$) on likelihood of survey respondents rating an endpoint higher or lower on relevancy to clinical practice (CP) or perception of evidence level (EL) based on ordinal logistic regression analysis

Endpoint	Demographic factor	OR	p-Value	Adequate model
Facilitation of wound closure (CP)	Setting: System (VA, US Military or hospital)	1.75	0.0004	Yes
Time to next therapy (CP)	Setting: Wound care center respondents	1.85	0.00012	No
Reduction of bioburden (CP)	Setting: Research respondents	0.33	0.00017	Yes
Reduction in antibiotic use (CP)	Wound care certified respondents	1.82	0.0003	Yes
Percent reduction of necrotic material (CP)	Specialty: Physician respondents	0.5	0.0005	Yes
Wound bed preparation (CP)	Wound care certified respondents	2.51	<0.00001	No
Perfusion (CP)	Setting: Wound care center respondents	2.13	0.0002	Yes
Facilitation of wound closure (EL)	Survey 1: High-level expert respondents	3.71	0.00017	Yes
Time to next therapy (EL)	Survey 1: High-level expert respondents	4.26	0.00002	Yes
Reduction in antibiotics (EL)	Survey 1: High-level expert respondents	4.47	0.00008	Yes
Wound bed preparation (EL)	Setting: Wound care center respondents	2.04	0.00005	Yes
Perfusion (EL)	Survey 1: High level expert respondents	2.94	0.00028	Yes
Cost effectiveness in terms of ulcer-free days (EL)	Wound care certified respondents	3.80	<0.00001	Yes
Edema reduction (EL)	Setting: Wound care center respondents	1.87	0.00036	Yes

DISCUSSION

Wound care has evolved into an interdisciplinary medical practice aimed at improving patient-centered outcomes beyond the traditional endpoint (failing paradigm) of complete epithelialization. Regulatory and reimbursement authorities are concerned that clinical trials of wound interventions assess criteria that are clinically important and meaningful. The WEF-CEP initiative established the content validated relevance of 22 of 28 published outcomes aside from complete wound closure, the traditional regulatory endpoint, surveying 628 interdisciplinary wound experts practicing in different settings with a variety of expertise.

Our study generally demonstrated consensus on the relevance and utility of WEF-CEP identified wound outcomes in supporting clinical practice and relevance to benefitting patients' lives using patient centered outcomes. However, some endpoints were perceived to have limited evidence supporting their use, and this gap will be addressed in a part 2, follow-up publication to this paper, for the 15 highest priority endpoints selected for further research.

A number of endpoints were not content validated in the survey, including *time to graft or flap*, *reduced time to re-harvest*, *facilitates wound closure*, *biomarkers*, *reduced scar*, and *time to next therapy*. It is conjectured that most wound care practitioners either do not use these concepts in their practice—or may not be familiar with them—and/or wound care researchers do not feel that they have been studied sufficiently to be considered as endpoints.

Some demographic groups among respondents also rated certain endpoints as more relevant than others, perhaps due to training or regional practice differences. For example, the endpoint *reducing antibiotic use* was more likely to have a higher score from high-level expert respondents or those with wound certifications, who may have

heightened awareness of the growing threat of antibiotic resistance.

The correlation between perceived relevance to clinical practice and evidence level was generally poor with the highest correlations for 3 endpoints (just above 0.3): *reduction in scar*, *odor reduction*, and *reduction in bioburden*. While this may be a reflection of respondents' beliefs that the evidence level of wound care endpoints is generally low, it might also be due to lack of knowledge in regard to evidence-based medicine as applied to wound care. For example, only those wound care researchers who are active in evidence-based medicine and familiar with the literature in regard to each endpoint might be expected to truly understand the relevant evidence levels and to date few systematic reviews have been published on endpoints not associated with complete wound healing.

Among the 15 highest priority endpoints, only *time to heal* (included as part of accelerated healing claim in FDA Guidance) is currently accepted as a primary outcome in Phase 3 and postmarket trials. Although *reduced pain* or *reduced infection* are recognized as secondary outcomes in the 2006 FDA Guidance document,⁶ they cannot be currently used as primary outcomes supporting regulatory clearance of a new wound intervention. Consequently, it can be seen that wound care researchers are extremely limited in current trials in regard to endpoint selection.

A closer look at the 15 highest priority, measurable endpoints reveals that several are related, offering opportunities to condense the list of validated endpoints into a few independent, highly relevant endpoints for regulatory consideration. Several examples are:

Percent area reduction and *percent volume reduction* assessed during the first 4–8 weeks of standardized wound management are related metrics; either or both could be a

clearly defined wound endpoint used in clinical studies to document *percent reduction in wound size*.

Cost of treatment is only part of the value equation in wound care; the most expensive intervention is the one that does not work.¹⁸ Using clearly defined standardized costs of treatment as the numerator in the *cost effectiveness* metric with units of a similarly specified endpoint as the denominator outcome, would represent value derived by using a standardized protocol of care, measuring cost per unit outcome delivered. Although the FDA is currently prohibited by law from including the cost of a drug, biologic, or device as part of its approval process, pressure continues to build to incorporate cost.

Though *reduced bioburden* parallels healing, more scientific clarity is needed about its relationship to host, microorganism, and environmental variables before one can consistently interpret high bioburden without clinical signs of infection.¹⁹ Moreover, as yet, the concept of wound bioburden is not one fully accepted at the FDA. The entire field of wound-related microbiology is rapidly changing and although reduced infection is recognized as a secondary endpoint, reduced bioburden requires greater specificity before it can be used as an endpoint. *Reduced infection* is already recognized as a secondary endpoint in the FDA 2006 Guidance.⁶

Improved function and ambulation, reduced isolation, and reduced depression are all part of several validated wound-related quality of life (QoL) scales.^{20–22} Recognizing each of these as valid, reliable endpoints contributing to QoL could support creation of one unified QoL endpoint, with an improvement in any one endpoint contributing to improved quality of life.

Reduced pain is one of the most-studied endpoints in clinical studies. Pain serves double duty as an adverse consequence of injury or surgery to be appropriately addressed intra- and postoperatively, and as a warning of tissue damage and/or infection. Thus, reduced pain indicates reversal or improvement in tissue damage, infection or appropriate treatment of an injury. The parallel, content-validated endpoint *reduced analgesic use* is related to *reduced pain*, and could be useful as a surrogate or supporting metric for this endpoint already recognized as a secondary outcome in the FDA 2006 Guidance.⁶ However, *reduced analgesic use* is independently important in relation to efforts to reverse the United States epidemic of dependence on analgesics. Together or separately these 2 endpoints may be considered metrics for pain management.

In addition to *time to heal*, which is already recognized as an FDA primary outcome, condensing the above endpoints would yield the 8 outcomes below for consideration as primary wound outcomes. The first four are already included in the 2006 FDA Guidance document;⁶ however, only complete wound closure is recognized by the FDA as a single primary outcome to demonstrate efficacy in clinical research. The second four in **bold** represent possible wound care outcome targets for FDA consideration as primary outcomes that have been content validated as important to both clinical practice and patients' lives:

1. Reduced pain (currently recognized as a secondary endpoint in wound care studies)
2. Reduced infection (currently recognized as a secondary endpoint in wound care studies)

3. Percent area reduction after 4–8 weeks of care (currently used to screen out rapidly healing patients not needing healing accelerants)
4. Reduced recurrence (included at 2 weeks in the 2006 FDA Guidance document⁶ to confirm healing)
5. **Reduced amputation** (likelihood or levels of amputation)
6. **Reduced economic burden** (improved cost effectiveness or reduced costs to patients)
7. **Improved function and ambulation** (vital to independence and mobility)
8. **Improved quality of life** (including social isolation, depression, odor, pain, improved function)

In a subsequent paper we will present the supporting evidence for these outcomes and address the need for further research.

Additional endpoints with high mean relevance ratings for CP and PCO that were also content validated were *reduced edema* and *reduced antibiotic use*. These endpoints, which reflect current medical practice, merit further consideration and research as recognized, content-validated endpoints important to both clinicians and patients in managing infection and tissue injury and merit consideration as potential primary or secondary endpoints.

The survey results highlight the endpoints that health-care professionals and educators in the field of wound care believe are relevant to clinical practice or patients' lives. While complete healing is important, other outcomes such as percent area reduction after 4–8 weeks of care, reducing pain, infections, or amputations can be more important to patients and their caregivers. The emphasis on complete healing per the 2006 FDA Guidance document should be updated to reflect meaningful real-world clinical goals to meet important patients and clinicians needs.

Wound care, like other medical fields, has evolved toward using more patient-centered outcomes as well as a broader range of outcomes now recognized to support clinical decisions. One lesson learned from these observed discrepancies between the 2006 FDA Guidance document and survey results is that primary endpoints requiring complete healing has biased enrollment away from typically ill patients toward including only those likely to heal completely during a RCT.²³ Endpoints rated important to clinicians or patients in terms of reducing amputation, morbidity, mortality, costs of hospitalization or surgery are recognized as vital to clinical success. Endpoints that address the needs of older or sicker patients less likely to heal have been neglected in evaluating drug, device or biologic wound care interventions.²⁴ Focusing solely on complete healing thwarts development of advances in wound care interventions that professionals believe help their patients most. Refocusing wound care on more clinically relevant measures of drug, device, or biological intervention success that are congruent with patient needs will help the FDA meet its mission to be "Responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable."⁷

Identification of alternative endpoints in wound care that represent clinical or patient-centered outcomes and their content validation is a first step toward offering them to the FDA for approval in clinical trials. The next steps

of this project will center on assembling the evidence for the 15 highest priority endpoints that have been chosen as the primary group, and determining their reliability in regard to stable patients, construct validity, and longitudinal evaluation of measurement properties/interpretation methods.¹¹

This study had a number of strengths, including a large number of respondents, high response rates, presentation of a wide cross-section of endpoints relevant to wound care, and method of assessing content validity. However, the study has some limitations. First, survey ratings for relevance to patients' lives in regard to patient-centered outcomes reflect clinicians' perception of what is important to patients; patient surveys would ideally be conducted to content validate the patient-centered endpoints relevant to include in clinical trials. Second, it is important to note that the adequacy of the evidence level rated by survey respondents was based on each respondent's perception; these ratings do not necessarily reflect evidence in the existing literature. Third, despite our best efforts to obtain a good cross-sectional survey of the wound care community, selection bias is still possible, which could affect the nature of the results.

CONCLUSION

Wound care has moved beyond the narrow focus of its past on complete wound healing as a primary outcome, to deliver outcomes that important to patients and clinical practice, even if the wound does not completely epithelialize. We surveyed 13 specialties and 9 settings to identify 15 wound care endpoints that were content validated suitable for the next steps of research needed to support FDA consideration as primary outcomes for use in clinical studies. This is an important first step in changing the current limitation of having complete healing as the only primary endpoint in FDA-approved clinical trials.

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REFERENCES

- Snyder RJ, Hanft JR. Diabetic foot ulcers—effects on QOL, costs, and mortality and the role of standard wound care and advanced-care therapies. *Ostomy Wound Manage* 2009; 55: 28–38.
- Armstrong DG, Boulton AJ, Andros G, Attinger C, Eisenbud D, Lavery LA, et al. Defining success in clinical trials of diabetic foot wounds: the Los Angeles DFCon consensus. *Int Wound J* 2009; 6: 211–3.
- Maida V, Ennis M, Kuziemyk C, Corban J. Wounds and survival in noncancer patients. *J Palliat Med* 2010; 13: 453–9.
- Escandon J, Vivas AC, Tang J, Rowland KJ, Kirsner RS. High mortality in patients with chronic wounds. *Wound Repair Regen* 2011; 19: 526–8.
- Eaglstein WH, Kirsner RS, Robson MC. Food and Drug Administration (FDA) drug approval end points for chronic cutaneous ulcer studies. *Wound Repair Regen* 2012; 20: 793–6.
- U.S. Food and Drug Administration. Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment, 2016. Available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071324.pdf> (accessed September 29, 2016).
- U.S. Food and Drug Administration. Statement of FDA Mission, 2016. Available at <http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm298331.pdf> (accessed September 29, 2016).
- Wei EX, Kirsner RS, Eaglstein WH. End points in dermatologic clinical trials: a review for clinicians. *J Am Acad Dermatol* 2016; 75: 203–39.
- Schaper NC, Apelqvist J, Bakker K. Reducing lower leg amputations in diabetes: a challenge for patients, healthcare providers and the healthcare system. *Diabetologia* 2012; 55: 1869–72.
- Tentolouris N, Al-Sabbagh S, Walker MG, Boulton AJ, Jude EB. Mortality in diabetic and nondiabetic patients after amputations performed from 1990 to 1995: a 5-year follow-up study. *Diabetes Care* 2004; 27: 1598–604.
- U.S. Food and Drug Administration. Clinical Outcome Assessment Qualification Program, 2016. Available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm> (accessed September 29, 2016).
- U.S. Food and Drug Administration. Clinical Outcome Assessment: Glossary of Terms, 2016. Available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm370262.htm> (accessed September 29, 2016).
- U.S. Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, 2016. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf> (accessed September 29, 2016).
- Walton MK, Powers JH, 3rd, Hobart J, Patrick D, Marquis p, Vamvakas S, et al. Clinical outcome assessments: conceptual foundation-report of the ISPOR Clinical Outcomes Assessment—Emerging Good Practices for Outcomes Research Task Force. *Value Health* 2015; 18: 741–52.
- Haynes SN, Richard DCS, Kubany ES. Content validity in psychological assessment: a functional approach to concepts and methods. *Psychol Assess* 1995; 7: 238–47.
- Lynn MR. Determination and quantification of content validity. *Nurs Res* 1986; 3: 382–5.
- Polit DF, Beck CT, Owen SV. Is the CVI an acceptable indicator of content validity? Appraisal and recommendations. *Res Nurs Health* 2007; 30: 459–67.
- Bolton L, van Rijswijk L, Shaffer F. Quality wound care equals cost effective wound care: a clinical model. *Nurs Manage* 1996; 27: 30, 32, 33,37.
- Bruce J, Russell EM, Mollison J, Krukowski ZH. The quality of measurement of surgical wound infections as the basis for monitoring: a systematic review. *J Hosp Infect* 2001; 49: 99–108.

20. Franks PJ, Moffatt CJ. Health related quality of life in patients with venous ulceration: use of the Nottingham health profile. *Qual Life Res* 2001; 10: 693–700.
21. Price P, Harding K. Cardiff Wound Impact Schedule: the development of a condition-specific questionnaire to assess health-related quality of life in patients with chronic wounds of the lower limb. *Int Wound J* 2004; 1: 10–17.
22. Blome C, Baade K, Debus ES, Price P, Augustin M. The “Wound-QoL”: a short questionnaire measuring quality of life in patients with chronic wounds based on three established disease-specific instruments. *Wound Repair Regen* 2014; 22: 504–14.
23. Carter MJ, Fife CE, Walker D, Thomson B. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. *Adv Skin Wound Care* 2009; 22: 316–24.
24. Gould L, Abadir P, Brem H, Carter M, Conner-Kerr T, Davidson J, et al. Chronic wound repair and healing in older adults: current status and future research. *J Am Geriatr Soc* 2015; 63: 427–38.