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A Randomized Controlled Trial Determining Variances in Ostomy Skin Conditions and the Economic Impact (ADVOCATE Trial)

Janice C. Colwell ◆ Joyce Pittman ◆ Rose Raizman ◆ Ginger Salvadalena

ABSTRACT

PURPOSE: To compare ostomy-related costs and incidence of peristomal skin complications (PSCs) for ceramide-infused ostomy skin barriers and control skin barriers.

DESIGN: The ADVOCATE trial is a multi-centered randomized controlled trial, and double-blinded international study with an adaptive design.

SUBJECTS AND SETTING: The sample comprised 153 adults from 25 sites from the United States, Canada, and Europe. Participants were seen in hospital and outpatient care settings.

METHODS: Data were collected by investigators at each site during face-to-face visits and during telephone check-in calls between visits. Cost of care data were collected using a questionnaire developed specifically for the study. The peristomal skin was assessed using the Ostomy Skin Tool. Health-related quality of life was measured using the SF-12v2. Patient-reported outcomes were collected using a patient-centered study-specific questionnaire. Cost of care was analyzed via analysis of covariance comparing total cost of care for 12 weeks between the 2 groups. The incidence of PSC was analyzed via Barnard's exact test comparing the incidence of PSCs between the control and treatment groups. Tertiary outcomes were exploratory in nature and not statistically powered.

RESULTS: Use of the ceramide-infused barrier significantly reduced stoma-related cost of care over a 12-week period, resulting in a $36.46 decrease in cost (14% relative decrease). The adjusted average costs were $223.73 in the treatment group and $260.19 in the control group ($P = .017$). The overall incidence of PSCs in the study was 47.7%; PSC incidence was 40.5% for the treatment group versus 55.4% for controls ($P = .069$, 95% confidence interval of the difference: −1.2 to 30.4). Significantly more participants using the ceramide-infused skin barrier were "very satisfied" with barrier performance (75% vs 55%; $P = .033$), prevention of leakage (63% vs 38%; $P < .01$), and prevention of itching (53% vs 31%; $P = .016$). General postoperative improvement in health-related quality of life was noted in both groups.

CONCLUSIONS: The use of a ceramide-infused barrier significantly decreased cost and increased satisfaction with patient-reported outcomes.

KEY WORDS: Adaptive design, Ceramide infused skin barrier, Cost, Ostomy, Patient outcomes, Peristomal complications incidence, Peristomal skin complications, Quality of life, Randomized controlled study, Skin barriers, Stoma.

Janice C. Colwell, MS, RN, CWOCN, FAAN, *University of Chicago Medicine, Chicago, Illinois.*

Joyce Pittman, PhD, RN, ANP-BC, FNP-BC, CWOCN, *Indiana University Health Academic Health Center, Indianapolis, Indiana.*

Rose Raizman, RN-EC, PHCNP, CETN(C), MSc, MNurs, *Scarborough and Rouge Hospital, Toronto, Ontario, Canada.*

Ginger Salvadalena, PhD, RN, CWOCN, *Hollister Incorporated, Libertyville, Illinois.*

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Conflicts of interest: Rose Raizman is on advisory board for Coloplast. Janice Colwell is a Hollister speaker and Coloplast speaker and consultant. Ginger Salvadalena is employed by Hollister Incorporated. Joyce Pittman is a Hollister-past grant recipient & speaker; and a past consultant for Coloplast.

Correspondence: *Janice C. Colwell, MS, RN, CWOCN, FAAN, University of Chicago Medicine, 5841 S, Maryland Ave, MC1083, Chicago, IL 60637 (janice.colwell@uchospitals.edu).*

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INTRODUCTION

Approximately 800,000 people are currently living with an ostomy and about 120,000 new ostomies are created annually in the United States and Canada.[1-3] Up to 80% of patients experience ostomy complications[4-8] and these predominantly consist of peristomal skin complications (PSCs). Best practice in the prevention of PSCs includes preoperative stoma site marking, ongoing involvement of a stoma care nurse, and the correct use of well-fitting ostomy products.[9] Despite these best practices, PSCs persist, and new strategies to reduce or eliminate their occurrence are needed.

Healthy peristomal skin is intact and free of visible signs of infection or other complications. Peristomal skin complications (PSCs) can be defined as skin inflammation, injury, or damage that occurs within the 3 to 4 inches of skin surface surrounding an abdominal stoma or skin covered by the adhesive portion of the pouching system (barrier and tape). PSCs are attributable to a variety of causative factors: mechanical, chemical, infectious, and systemic health conditions.[10] The most common cause of PSCs is peristomal

moisture-associated damage, often resulting from exposure of the skin to stoma effluent.[11] Another cause of PSCs is mechanical damage consisting of medical adhesive-related skin injury associated with removal of pouching systems.[12] Reported prevalence rates of PSC are as high as 70%.[8,10-17] Regardless of the cause, PSCs significantly impact patient's lives and can lead to pain, reduce life satisfaction, and increase health care costs.[2,4,6,11,18]

The cost of ostomy care has historically been difficult to evaluate due to high variability across countries and regions, pouch change practices, product costs, and care delivery models. It is generally believed that PSCs increase usage of pouching supplies, clinic visits, and other services, increasing the cost burden of ostomy-related care across health care systems. Peristomal skin complications also affect enjoyment of life. In a study of 239 veterans, Coons and colleagues[19] reported that 16% had difficulty paying for ostomy supplies and difficulty paying was a significant predictor of overall quality of life. Current estimates of usual ostomy supply cost in the United States range $100 to $300 per month depending on insurance coverage and usage.[20] Peristomal skin problems may create difficulty keeping a pouching system in place and lead to higher product utilization and cost.[18] Clearly, maintaining peristomal skin integrity has important implications for the health care economic environment and the individual with an ostomy.

A potential method of maintaining peristomal skin integrity is the infusion of specific ingredients into the ostomy skin barrier.[21] The treatment product in this study is a skin barrier infused with ceramide. Ceramides are naturally occurring lipids that are essential to the barrier function of the skin and lipid bilayer of the stratum corneum.[22] They serve an important role in the prevention of transepidermal water loss by fusing with corneocytes in the stratum corneum to help form a protective layer. An ostomy skin barrier infused with ceramide may assist in protecting peristomal skin health by reducing the incidence, severity, and or duration of PSCs, resulting in lower cost of care.

The purpose of the ADVOCATE trial was to compare stoma-related costs and incidence of PSCs between 2 types of ostomy skin barriers. The primary objective was to compare stoma-related costs with use of skin barriers containing ceramide (treatment) to skin barriers without ceramide (control). The secondary objective was to compare the incidence of PSCs for the 2 groups. Additional tertiary measures were also captured including patient-reported outcomes (eg, itching and comfort) and health-related quality of life.

METHODS

The ADVOCATE trial was a multicentered randomized, controlled, and double-blinded international study with an adaptive design. The adaptive design is derived from Mehta and Pocock[23]; it is based on conducting one or more preplanned interim analyses to assess the initial sample estimate, which is adjusted as necessary. Furthermore, the adaptive design allows for early study conclusion depending upon the significance level of interim findings. Using published cost estimates[18] the study was powered to detect a 50% difference in PSC-related costs between groups (at 80% power and 5% error), resulting in a target sample size of 144 subjects. A preplanned interim analysis was conducted at the completion of 92 subjects; based on the interim results, the subsequent (and ultimately final) analysis occurred at the completion of 153 subjects.

The analysis included eligible subjects who completed the study between March 2015 and January 2017. Twenty-five sites participated from the United States (15), Canada (4), and Europe (6), conducting study visits in hospital and outpatient settings. Institutional Review Board or Ethics Committee approval for this study was obtained for each participating site, and the study was conducted in accordance with ICH-GCP. The study is listed on http://www.ClinicalTrials.gov as NCT02401412: A Study Determining Variances in Ostomy Skin Conditions and The Economic Impact.

Adults (18 years or older) who were within 12 weeks after creation of a colostomy, ileostomy, or urostomy and who had normal peristomal skin were deemed eligible to participate. To determine eligibility, the peristomal skin was assessed using the Ostomy Skin Tool[24] and healthy skin was defined by a discoloration, erosion, and tissue overgrowth (DET) score of zero (or a DET score > 0 if due to normal postoperative healing and/or scar tissue). Exclusion criteria included peristomal fistulae, wounds (eg, mucocutaneous separation), lesions (such as suture granuloma), infection of the peristomal area, tape allergy, and individuals who were residing in long-term care facilities (due to difficulty in capturing stoma cost data). Pregnant or nursing mothers were also excluded.

Trained investigators recruited participants from their clinical practice settings. Study investigators were health care providers experienced in ostomy care, most of whom were certified WOC nurses, enterostomal therapy (ET) nurses, or stoma care nurses. Participants were provided with information regarding the study, and written informed consent was obtained from all participants before data were collected. Participants were informed that they could withdraw from the study at any time.

Participants were randomized to treatment or control skin barrier in a 1:1 ratio via a randomized block design stratified by study site; randomization was performed using the electronic data capture system (Figure 1; Medrio, San Francisco, California). Before randomization, the investigator indicated whether the participant should receive standard-wear barrier or extended-wear barrier if randomized to the control arm.

All data were collected by trained investigators during face-to-face visits (initially and then every 4 weeks for a total of 3 in-person visits unless a PSC occurred) and during telephone check-in calls between visits. Investigators entered data into an electronic data capture system (Medrio, San Francisco, California). The nursing assessment consisted of an observation of the peristomal skin with the pouching system removed, and completion of questionnaires as described later. At any assessment, if a subject sustained a PSC, the investigator scheduled 2 additional study visits at 2-week intervals during the 4-week PSC resolution period. This flow through the study was designed to mirror best practices for the management of patients with new stomas, increasing the frequency of visits when management of complications was required.

Costs of care data were collected at each study visit using a questionnaire developed specifically for the study. Questionnaire items included treatments related to ostomy and/or PSCs (topical medications, clinic visits, and selected accessory use), social impact of ostomy and/or PSCs (missed work/appointments), ostomy-related hospitalizations, emergency department visits, physician/clinic visits, medication use and therapies, and product utilization.

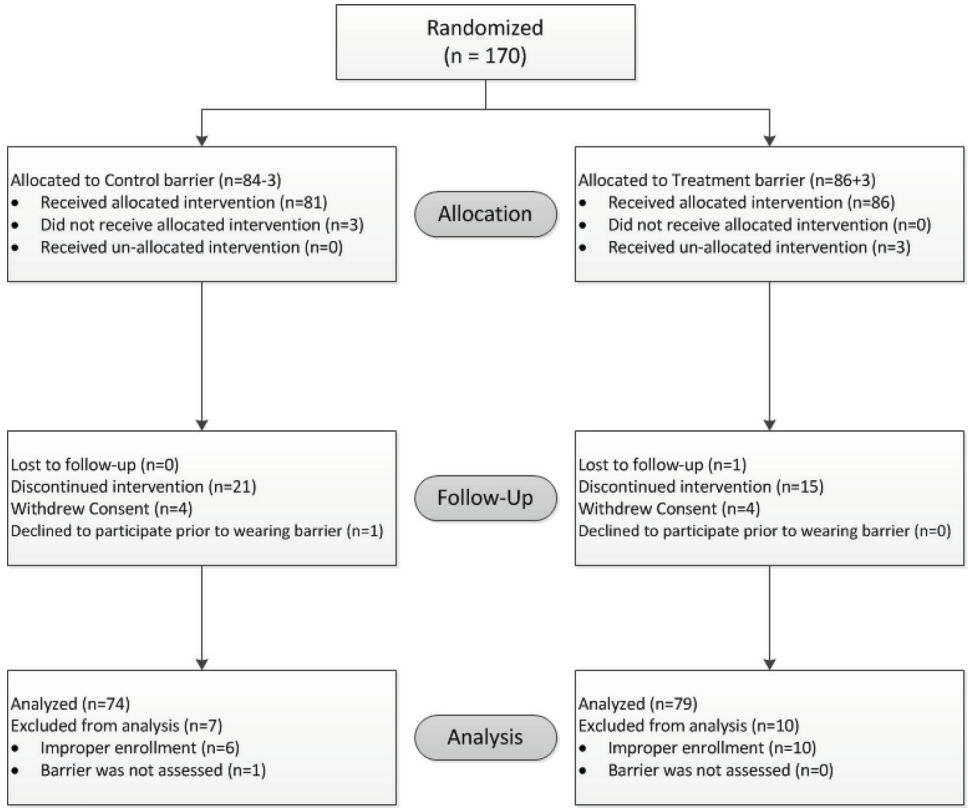

Figure 1. Study flow diagram.

Each in-person clinical evaluation consisted of a visual assessment of the stoma and peristomal skin and photography of the peristomal area. The skin assessment portion of the validated Ostomy Skin Tool[24] was used to describe the status of the peristomal skin. Investigators assigned a number reflecting the presence and extent of any DET at each clinical evaluation, resulting in a score indicating the peristomal skin status. The Ostomy Skin Tool demonstrates moderate to good internurse assessment agreement ($\kappa = 0.54$) and higher agreement between experts nurse assessors ($\kappa = 0.70$).[25] Subjects were deemed to have had a PSC if the DET score was above zero due to anything other than normal postoperative healing and/or scar tissue, or the DET score increased above the normal score obtained at a previous visit. All investigators received training on the use of the DET instrument during the site initiation visit and as indicated thereafter. Peristomal photographs were uploaded to the electronic database and reviewed centrally by WOC nurses to monitor congruence with assigned DET scores.

Participants completed a quality-of-life questionnaire at their first visit and again during their final study visit using the SF-12v2 Health Survey (QualityMetrics Incorporated & Medical Outcomes Trust, 2002). The reliability and validity for the SF-12v2 have been reported for a range of medical conditions.[26] Patient-reported outcome measures were collected at the final visit using a patient-centered study-specific questionnaire. Items included ease of product application and removal and satisfaction with wear time, prevention of leakage, prevention of itching, and overall satisfaction with the skin barrier.

Participants were instructed to change their pouching system according to their health care provider's recommendations. Likewise investigators recommended barrier shape, sizing, and accessory use at each visit throughout the course of the study. Subjects were enrolled into an 8-week observation period comprising a nursing assessment every 4 weeks. All participants were provided with ostomy care and teaching per the site's standard of care, and participants who were randomized to treatment used 2-piece pouching systems with ceramide-infused skin barrier (CeraPlus skin barrier with Remois Technology, Hollister Incorporated, Libertyville, Illinois, Remois is a technology of Alcare Co, Ltd). Participants randomized to control used 2-piece pouching systems with a standard-wear or extended-wear skin barrier (FlexWear or Flextend, Hollister Incorporated). The investigators and participants were blinded to the type of assigned skin barrier used. Skin barriers were similar in appearance and were labeled without brand names. The first barrier was applied during the first study visit, and additional product was provided to the subject for continued use throughout the study.

Data Analysis

The main outcome (difference between total cost of care between treatment and control groups) was analyzed via analysis of covariance (ANCOVA). To adjust for any impact, the cost of care for 12 weeks was adjusted for body mass index, ostomy type and duration, presence of hernia, and investigator site. Cost data included for analysis of the primary objective were barriers, topical steroid, antifungal powder, antibiotic (oral, intravenous, or topical), adhesive remover, skin barrier powder, skin films, belts, adhesive spray, and any unplanned/extra stoma-related health care provider visit. Skin barrier rings, paste, and pouches were not included in the analysis of cost of care, as their primary function is for product fit. All costs

were calculated in 2015 US dollars, and skin barrier costs were standardized to the lowest reimbursed amount to remove any artificial or country-specific cost variances between the skin barriers. Supply and medication costs were standardized to generic forms to remove over- or understating costs. Because of variable follow-up time among subjects (1-97 days), costs were modeled to create a standard period of 12 weeks.

The secondary objective (comparing the incidence [proportions] of PSCs between treatment and control groups) was analyzed via Barnard's exact test. A PSC was deemed to have occurred if there was an increase in the DET score from the participants' baseline. Time to event data (eg, time to occurrence of PSC and time to resolution of PSC) was analyzed via standard descriptive measures and the Wilcoxon-Mann-Whitney *U* test. Health-related quality-of-life data were analyzed via descriptive measures and ANCOVA. Analyses of qualitative and quantitative tertiary variables, such as subject satisfaction with the barrier, were analyzed via standard descriptive measures, 2-sample *t* tests, and Fisher exact tests.

At the interim analysis (92 subjects), differences in primary and secondary objectives were evaluated and conditional power was calculated to assess the appropriateness of the initial sample size estimate. The revised estimated sample size was 210 subjects; a second interim analysis was planned at 152 subjects. At the next interim analysis (153 subjects), the study was stopped after meeting the predetermined significance ($P \leq .026$) for the primary objective. Thus, this analysis was considered the final analysis. A level of $P < .05$ was considered significant for variables not included in any interim analyses.

RESULTS

Data from 153 eligible subjects (79 treatment and 74 control) were included in the final analysis. Table 1 displays baseline characteristics of the 153 participants. No statistical differences were found between control and treatment groups based on univariate comparison of these demographic and pertinent clinical characteristics.

TABLE 1.
Baseline Demographic and Pertinent Clinical Characteristics

	Control n (%)	Treatment n (%)	*P* Value
Participants	74 (48.4)	79 (51.6)	
Gender			$P = .61$[a]
• Male	43 (58.1)	50 (63.3)	
• Female	31 (41.9)	29 (36.7)	
	Mean (SD)	**Mean (SD)**	
Age	57.2 (15.2)	55.4 (15.5)	$P = .46$[b]
BMI	26.4 (5.8)	24.8 (5.8)	$P = .09$[b]
Stoma duration, wk	5.5 (3.6)	4.7 (3.4)	
Stoma type	**n (%)**	**n (%)**	$P = .97$[a]
• Colostomy	40 (54.0)	41 (51.9)	
• Ileostomy	27 (36.5)	31 (39.2)	
• Urostomy	7 (9.5)	7 (8.9)	

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]Fishers exact.
[b]Two–sample *t* test.

Cost of Care and PSCs

The adjusted average 12-week total ostomy-related cost of care in the treatment group was $223.73, and it was $260.19 in the control group (Table 2). This difference of $36.46 between the 2 groups ($P = .017$; 95% confidence interval, 6.49 to 66.43) represents a 14% relative reduction in costs with the treatment skin barrier.

Seventy-three study participants developed a PSC; the incidence of PSCs was 40.5% in the treatment group and 55.4% in the control group. The difference in PSC incidence of 14.9% was not statistically significant ($P = .069$; 95% confidence interval, −1.2 and 30.4) but based on the observed difference; there was a 26.9% relative reduction in PSCs with use of the treatment skin barrier (Table 2). Significantly more PSCs resolved within 4 weeks with the treatment skin barrier (treatment 53% vs control 29%; $P = .042$).

Patient-Reported Outcomes

Significantly more subjects in the treatment group were "very satisfied" with overall barrier performance than were participants in the control (75% vs 55.2%; $P = .033$). Significantly more subjects in the treatment group reported being "very satisfied" with the prevention of leakage (63.3% vs 37.9%; $P < .01$) and prevention of itching (53% vs 31%; $P = .016$). Additional findings for satisfaction measures and quality-of-life measures are shown in Table 3.

DISCUSSION

The ADVOCATE trial is one of the few randomized controlled trials related to ostomy care. It is unique in its purpose—to evaluate the effect of ostomy skin barriers on cost and PSCs. Furthermore, the rigorous design included blinding of investigators and participants and was statistically powered for the primary objective. Tam and colleagues[27] conducted a meta-analysis of randomized controlled trials comparing interventions for peristomal skin care and found only 6 relevant randomized controlled trials. While they found no statistically significant benefit of adjunctive intervention therapies in reducing PSCs, they also found that the studies they identified were often underpowered. Therefore, the ADVOCATE trial provides important new information addressing a knowledge gap about the management of peristomal skin and the cost advantages of these improvements.

We found a statistically significant cost savings, favoring the treatment skin barrier. The costs included skin barrier and specified accessory utilization, medications, ostomy-related clinic and emergency department visits, hospitalization and social impact of ostomy, and/or PSCs (missed work/appointments). As such, the prospective collection of ostomy costs was highly relevant and provides a level of detail about resource utilization that has not been previously reported.

Peristomal skin complication incidence in this study sample was 47.7% (n = 73), and the incidence of PSCs was observationally lower in the treatment group than in the control. Other investigators have reported PSC incidence rates consistent with the current analysis; they ranged from 29% to 63%.[11,12,14-17] The wide range of reported PSC incidence may be partially due to a lack of consistency in the operational definitions used between investigators and differences in duration

TABLE 2.
Cost of Care/PSC Incidence

	Treatment (n)	Control (n)	Difference (*P*)	95% CI of Difference
Cost	$223.73 (79)	$260.19 (74)	$36.46 ($P = .017$)	6.49 to 66.43
PSC incidence	40.5% (32/79)	55.4% (41/74)	14.9% ($P = .069$)	−1.2 to 30.4

Abbreviations: CI, confidence interval; PSC, peristomal skin complication.

of subject follow-up. Even during the ADVOCATE trial, an amendment was made relevant to the use of the DET score to respond to investigator concerns that postoperative skin can be clinically normal in the presence of skin discoloration.

Patient satisfaction was generally positive for subjects in both groups. Findings of greater satisfaction with barrier overall performance, prevention of itching, and prevention of leakage are interesting and bear further investigation. Prevention of leakage is an important concern that can impact sleep, social interactions, and product usage.[28,29] Our findings related to health-related quality of life are consistent with other authors, who indicated it is negatively affected by time since surgery and PSC occurrences.[30,31]

STRENGTHS AND LIMITATIONS

A major strength of the ADVOCATE study is its design, which incorporated randomization and double blinding to the prospective comparison of one skin barrier to another. This design adds to the rigor of the study and strengthens the findings, controlling for clinician bias and subject prognostic differences. From a practical perspective, the study design incorporated regular assessment and intervention by an ostomy nurse specialist who made adjustments in product fit as appropriate, in congruence with best practices. In addition, a standard, validated tool was used for skin assessment to enhance the likelihood of reliable measurements across sites. Random allocation and allocation concealment helped reduce the risk of bias, strengthening the internal validity of the study. Incorporation of multiple sites from varied locations and countries strengthens the generalizability of the study findings overall.

An ongoing difficulty affecting study enrollment was the early and high incidence of PSCs in potential study candidates at many study sites, which limited the speed of recruitment. Similarly, other investigators have reported up to 80% of clinic patients[32] and 73% of survey respondents managed their own PSCs without seeking care from a health care professional.[33] A possible limitation was the use of only one manufacturer's skin barriers. The choice to use only one brand was made to enable blinding and remove brand bias. However, as controls, researchers had access to standard-wear and extended-wear barriers in flat and convex, presized and cut-to-fit options, along with accessories from any manufacturer. Thus, investigators had access to a wide variety of usual options for both control and treatment groups. Limitations may also include unknown differences in baseline characteristics between the 2 groups that contributed to the results we found. Lastly, given that costs were modeled to create a standard period of 12 weeks, limitations inherent to the modeling of cost data may apply.

CONCLUSIONS

The ADVOCATE study is the first randomized controlled trial with blinding and an adaptive design to compare the effect of ostomy skin barriers on cost of stoma care and PSCs. The ceramide-infused ostomy skin barrier was shown to lower costs and help to reduce PSCs. Peristomal skin health is key to reduction of complications and ultimately to the ostomy-related cost of care. These findings provide important information for clinicians caring for individuals with an ostomy regarding new solutions to clinical challenges of maintaining intact peristomal skin while managing costs.

TABLE 3.
Patient-Reported Outcomes

Item	Treatment	Control	Difference	*P* Value
Patient satisfaction with the barrier (n; %)[a]				
Overall performance	45; 75.0%	32; 55.2%	23.8%	.03
Prevention of leakage	38; 63.3%	22; 37.9%	25.4%	<.01
Prevention of itching	32; 53.3%	18; 31.0%	22.3%	.02
Adherence to the skin	41; 68.3%	30; 51.7%	16.6%	.09
Ease of removal	39; 65.0%	33; 56.9%	8.1%	.45
Wear time	41; 68.3%	30; 51.7%	16.4%	.09
Quality of life (SF-6D health index[b]) (mean; SD)				
Baseline visit	0.624; 0.14	0.643; 0.14	−0.019	.40
Final visit	0.729; 0.13	0.739; 0.13	−0.01	.69

SD, standard deviation; SF-6D, short form-6-dimension.
[a]Data were available for 108 patients; all percentages reflect the percentage of patients who stated they were "very satisfied" with the respective barrier attributes.
[b]SF-6D score adjusted for ostomy type, gender, and patient age.

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