Received: July 21, 2020 Revised: August 4, 2020 Accepted: August 10, 2020

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13267

# Health-Related Quality of Life Associated With Pain Health States in Spinal Cord Stimulation for Chronic Neuropathic Pain

**Rui V. Duarte, PhD*; Nicole Soliday, MPH†; Angela Leitner, MS†; Rod S. Taylor, PhD‡§**

## ABSTRACT

**Objectives:** A substantial proportion of patients have recently reported pain reduction levels of ≥80% following treatment with Evoked Compound Action Potential (ECAP) spinal cord stimulation (SCS). The additional health-related quality of life (HRQoL) utility gain that can be achieved in this patient group is unclear. The aim of this study is to quantify the HRQoL utility values seen in a remission health state (defined as ≥80% pain reduction) and contrast with more traditional health states of <50% and ≥50% pain relief.

**Materials and Methods:** Pain intensity assessed using a 100 mm visual analogue scale (VAS) and EQ-5D-5L questionnaires were collected from 204 patients treated with ECAP SCS for chronic back and leg pain and followed up to 12 months. Utility values were derived using EQ-5D-5L responses crosswalked to EQ-5D-3L. Linear regression models adjusted for baseline utility values and patient demographics were used to compare differences in utility values across health states.

**Results:** Patients in the remission health state (i.e., ≥80% pain reduction) consistently reported statistically significant greater utility values (+0.09 to +0.15, all $p < 0.003$) compared to patients reporting ≥50% pain relief at 3- and 12-month follow-up for overall, back, and leg VAS pain. The gain in utility values per percent unit of pain reduction was statistically significant at 3- and 12-month follow-up with a mean increase in HRQoL utility score between 0.003 and 0.005 observed for each percent of pain reduction.

**Conclusion:** Our analyses show that patients in a remission health state report statistically and clinically significant better HRQoL than patients experiencing lesser pain relief.

**Keywords:** Chronic pain, health states, health-related quality of life, remission, spinal cord stimulation

**Conflict of Interest:** Rui V. Duarte has received consultancy fees from Medtronic Ltd, Boston Scientific Corp and Saluda Medical. Nicole Soliday and Angela Leitner are employees of Saluda Medical. Rod S. Taylor has received consultancy fees from Medtronic Ltd, Saluda Medical, and Nevro Corp.

## INTRODUCTION

Health-related quality of life (HRQoL) is a commonly used outcome measure for clinical trials. The use of HRQoL tools as part of clinical trials allow to obtain health utility values which are used to inform economic evaluations and determine the cost effectiveness of an intervention. Utility values also can be assigned to health states in economic models that consider outcomes of importance for a specific population (1). To date, the health states used to inform model-based economic evaluations of spinal cord stimulation (SCS) have all considered patient experience with optimal (i.e., ≥50%) or suboptimal (i.e., <50%) reduction in pain.

The field of neurostimulation has seen numerous advances in recent years that include new waveforms (e.g., burst (2), high frequency (3), high density) (4), new neural target areas (e.g., dorsal root ganglion) (5), and, most recently, measurement of the neurophysiological response to SCS to confirm stimulation of the intended target within the therapeutic window to modulate neural activity that drives pain inhibition (i.e., Evoked Compound Action Potential [ECAP] SCS, closed-loop) (6). Traditionally, satisfactory pain relief following therapy has been defined as a reduction in pain rating of 30–50% or more. However, more recent clinical trials of SCS have reported a substantial proportion

Address correspondence to: Rui V. Duarte, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, Liverpool L69 3GB, UK. Email: rui.duarte@liverpool.ac.uk

* Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK;
† Saluda Medical Pty Ltd., Artarmon, NSW, Australia;
‡ Institute of Health and Well Being, University of Glasgow, Glasgow, UK; and
§ College of Medicine and Health, University of Exeter, Exeter, UK

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: This study was funded by Saluda Medical.

of chronic pain patients reporting pain reduction levels of ≥80% (6,7). In contrast to lower levels of pain relief, this group of "high responders" (or "remitters") have the potential ability to achieve considerably better levels of HRQoL.

However, it remains unclear what the additional extent of HRQoL utility gain might be achieved in this population. Furthermore, the cost effectiveness of newer SCS technologies may be underestimated by not formally including consideration of additional gains in health (and reductions in costs) associated with high responders. In addition, the probabilities of achieving different pain reduction thresholds and associated health state utility values has the potential to affect cost effectiveness estimates of SCS. Empirical research is therefore needed to determine the utility values associated with these pain health states to improve existing SCS economic models.

The aim of this study is to quantify the HRQoL utility values seen in remitters (i.e., ≥80% pain reduction) and contrast this with the values associated with the more traditional health states of <50% and ≥50% pain relief.

## MATERIALS AND METHODS

### Study Design

This study used data from a total of 204 patients from two previously reported studies (EVOKE [NCT02924129] and AVALON [ACTRN12615000713594]) in patients with chronic back and leg pain who received SCS using the Evoke SCS System (Saluda Medical) with follow up at 3- and 12-month postimplant. EVOKE was a multicenter, double-blind, parallel-arm randomized controlled trial (RCT) conducted in 13 centers in the US with 134 patients randomized 1:1 to closed-loop SCS or open-loop (i.e., conventional) SCS (6). AVALON was a multicenter, prospective single-arm study conducted in five centers in Australia with 70 patients screened (7). Both studies were conducted in compliance with ethical and regulatory guidelines and were approved by local ethics committees prior to subject enrolment.

### ECAP SCS

In SCS, electrodes are implanted in the epidural space over the dorsal aspect of the spinal cord and connected to a stimulator to deliver electrical stimulus with the goal of producing pain relief and other clinical benefits. SCS therapies, however, are limited in that stimulation occurs without knowledge of whether the intended target is activated or the level of such activation (8). They are further challenged by the constantly changing distance between the electrode and the spinal cord that occurs with both patient involuntary physiological and voluntary movement (9). These factors may contribute to the variability observed in clinical outcomes (10).

The Evoke System was designed to address these limitations by continuously recording *in vivo* human spinal cord electrophysiology to confirm modulation of neural activity that drives pain inhibition (11,12). An ECAP is measured for every stimulation pulse delivered, which reflects the type and degree of spinal cord activation elicited by SCS (see Supporting Information Material 1). Thus, the intended target is identified and the therapy delivered is confirmed. The system may operate in fixed-output, open-loop (open-loop) or ECAP-controlled, closed-loop (closed-loop) mode. ECAP measurement is performed in both modes and may be used to determine optimal stimulation settings. In closed-loop mode, the measured ECAP is compared to the target ECAP amplitude and the stimulation current is automatically adjusted to maintain consistent spinal cord activation.

### Demographic and Outcome Data

For the present study, we obtained the following individual patient data:

1. Patient demographics: age, gender, duration of pain, previous back surgery;
2. Pain intensity: overall, back, and leg pain visual analog scale (VAS) scores at baseline, 3- and 12-month follow-up;
3. HRQoL: EQ-5D-5L utility scores at baseline, 3- and 12-month follow-up.

Pain intensity was assessed using a 100 mm VAS ranging from 0 (no pain) to 100 (worst possible pain) (13). The VAS is considered a reliable and valid measure of subjective phenomena including chronic pain (13,14). Levels of pain relief were based on the health states currently used in economic models to assess the impact of SCS:

- "No pain relief" (NPR): no pain relief or worsening of pain;
- "Suboptimal pain relief" (SPR): pain relief up to 50%;
- "Optimal pain relief" (OPR): ≥50% pain relief.

In addition, we defined ≥80% pain relief as indicative of "high response" or "remittance" (R) (6,15,16).

HRQoL was derived from participants' responses to the EQ-5D-5L instrument. The EQ-5D-5L descriptive system is a questionnaire designed to be completed by the patient and comprising five dimensions (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety), where each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/ extreme problems (17). The respondent is asked to indicate his/her overall health state by selecting the level that corresponds to his/her quality of life for each of the five dimensions. Responses to the EQ-5D-5L were converted into single (utility) indices using a set of weights (tariff) reflecting population preferences for the particular health state. Utility scores were obtained by using the EQ-5D-5L responses crosswalked to the EQ-5D-3L UK value set (18). Results also are presented considering utility scores obtained using the US value set for EQ-5D-5L crosswalk to EQ-5D-3L (see Supporting Information Material 2).

### Statistical Analysis

Data on 170 patients provided 99% power at 5% alpha to detect a clinically important difference in EQ-5D utility of 0.10 between pain cut-offs assuming a standard deviation of 0.20 (19).

Probabilities of patients achieving the four different pain reduction thresholds (no pain relief, suboptimal pain relief, optimal pain relief, and remission) and associated HRQoL utility values (means and 95% confidence intervals [CIs]) were estimated at each threshold for EQ-5D data at 3- and 12-month follow-up.

Linear regression models were used to compare the differences in utility values across the pain reduction threshold. Given the observational nature of these analyses, models were adjusted for baseline utility values, patient age, gender, duration of pain, and previous back operation history. A secondary regression analysis was undertaken using pain reduction as a continuous variable. All



  

models were run separately for EQ-5D utilities at 3- and 12-month follow-up data and for overall, leg, and back pain.

All data analyses were undertaken using STATA v16.0.

## RESULTS

Between August 2015 and September 2016 (AVALON case series, $n$ = 70) and January 2017 and January 2018 (EVOKE RCT, $n$ = 134), a total of 204 patients were enrolled in the respective studies (Fig. 1). The 12-month follow-up assessment was completed by a total of 146 patients across both studies.

Participants in the studies had an average age of 55.6 years and relatively equal representation by sex, with a mean overall VAS pain of 81.3 and primarily a failed back surgery syndrome diagnosis (Table 1). The mean utility value with EQ-5D at baseline was 0.33.

At 3- and 12-month follow-up more than half of the patients experienced ≥80% pain relief (i.e., remission) for overall, back, and leg pain (Table 2). Optimal pain relief (i.e., ≥50% and <80%) was experienced by approximately a quarter of patients across the types of pain and follow-ups. Suboptimal pain relief (i.e., <50%) was achieved by between 11% and 21% of patients across the types of pain and follow-ups. Only a small number of patients (i.e., between 1% and 3%) did not obtain some degree of pain relief.

**Table 1.** Population Characteristics at Baseline.

| Characteristic | $N$ = 204 |
|---|---|
| Data source | |
| EVOKE trial—*N* (%) | 134 (66%) |
| AVALON study—*N* (%) | 70 (34%) |
| Age (years)—mean (SD) | 55.6 (11.4) |
| Gender—*N* (%) | |
| Male | 104 (51%) |
| Female | 100 (49%) |
| Duration of pain (years)—mean (SD) | 13.0 (10.2) |
| Previous back surgery—*N* (%) | 128 (63%) |
| VAS pain 0–100 (mm)—mean (SD) | |
| Overall | 81.8 (10.3) |
| Leg | 78.0 (14.3) |
| Back | 80.0 (12.2) |
| EQ-5D utility (UK values)—mean (SD) | 0.33 (0.23) |

SD, standard deviation; VAS, visual analog scale.

The mean (SD) utility values derived from the EQ-5D were 0.67 (0.20) at 3-month follow-up 0.65 (0.22) at 12-month follow-up.

Comparison of utility values derived from the EQ-5D between NPR and SPR health states shows no statistically significant

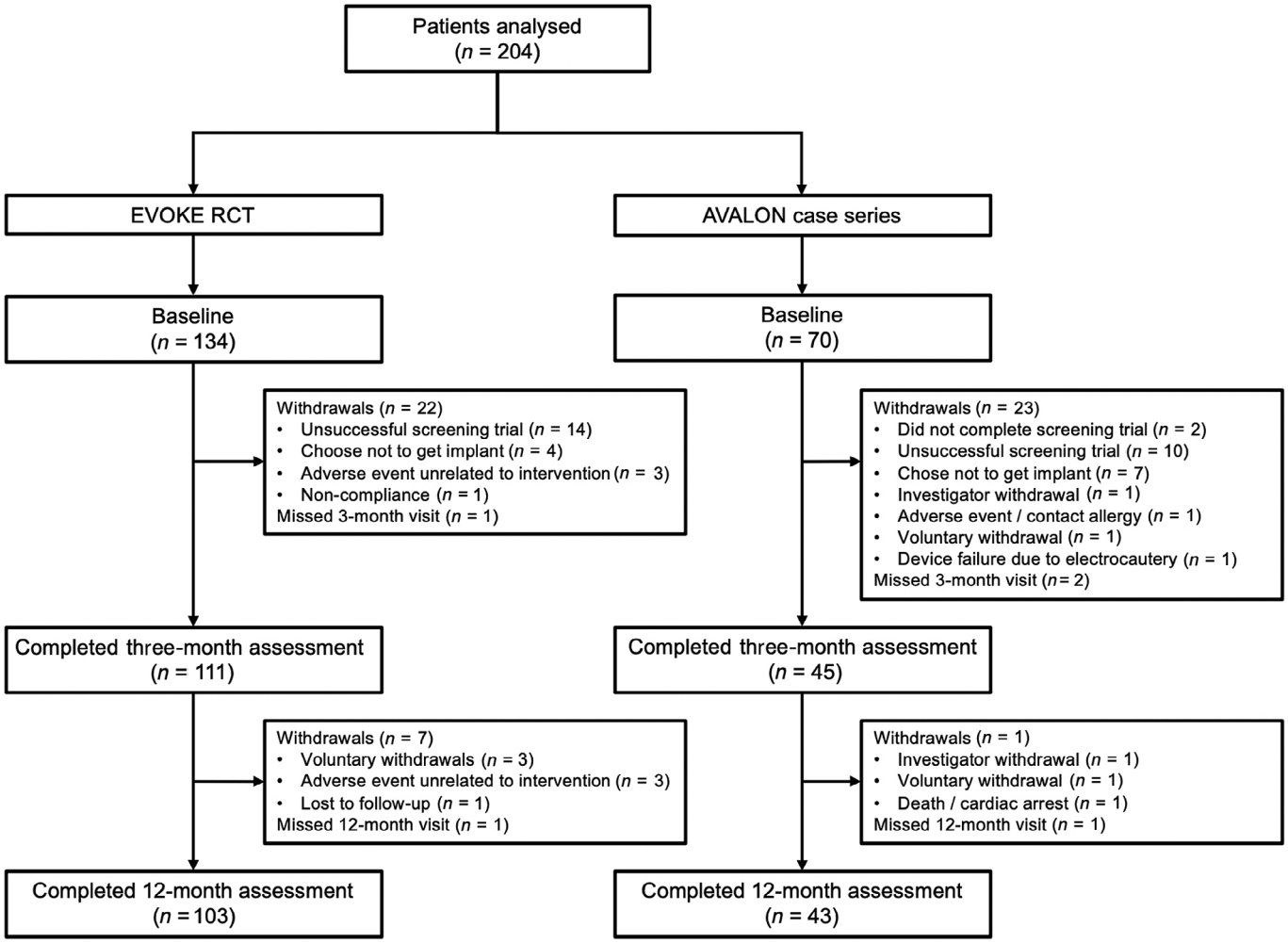


**Figure 1.** Study flow diagram.



  

**Table 2.** Level of Pain Relief by Health States at 3- and 12-Month Follow-Up.

| | Overall pain *n/N* (%) | | Back pain *n/N* (%) | | Leg pain *n/N* (%) | |
|---|---|---|---|---|---|---|
| | 3-month | 12-month | 3-month | 12-month | 3-month | 12-month |
| No pain relief (0%) | 2 (1%) | 2 (1%) | 2 (1%) | 4 (3%) | 4 (3%) | 3 (2%) |
| Suboptimal pain relief (<50%) | 28 (18%) | 19 (13%) | 33 (21%) | 24 (17%) | 17 (11%) | 18 (13%) |
| Optimal pain relief (≥50% to 80%) | 44 (28%) | 44 (30%) | 38 (25%) | 39 (27%) | 32 (22%) | 32 (23%) |
| Remission (≥80%) | 82 (53%) | 81 (55%) | 82 (53%) | 78 (54%) | 95 (64%) | 85 (62%) |
| Total | 156 | 146 | 155 | 145 | 148 | 138 |

differences for overall and back pain at 3- or 12-month follow-up (Table 3). A statistically significant difference is observed for NPR versus SPR for leg VAS pain at 12-month follow-up. Comparison of SPR versus OPR health states shows statistically significant greater utility scores for OPR health state at 3- and 12-month follow-up for overall and back VAS pain and at 12 months only for leg VAS pain. Patients in the R health state consistently reported statistically significant greater utility values than patients in the OPR health state at 3- and 12-month follow-up for overall, back, and leg VAS pain.

The gain in utility values per percent unit of pain reduction was statistically significant at 3- and 12-month follow-up for overall, back, and leg VAS pain (Table 4). A mean increase in HRQoL utility score between 0.003 and 0.005 is observed for each percent of pain reduction experienced in overall, back, or leg VAS pain. The $r^2$, which explains the variance in utility score due to pain relief observed, ranged from 0.25 (leg VAS pain at 3 months) to 0.42 (back VAS pain at 12 months).

Positive correlation coefficients between EQ-5D-5L utility values and pain reduction in overall VAS pain were 0.667 and 0.550 at 3-month follow-up (Fig. 2) and 12-month follow-up (Fig. 3), respectively. Similar correlation coefficient values were observed for back (0.613, 0.604) and leg (0.654, 0.500) VAS pain at 3- and 12-month follow-up, respectively.

Utility values derived from the EQ-5D-5L responses crosswalked to EQ-5D-3L US value set show greater index scores for all the different health states (Supporting Information Material 2). Differences between health states observed using the US value set are consistent with the results based on the UK value set.

## DISCUSSION

This study shows that the improvement in HRQoL utility of people with chronic pain is directly associated with their level of pain relief. Our results confirm that a "high response" or "remission" health state (i.e., ≥80% pain relief) is associated with greater HRQoL utility when compared with the more traditional level of ≥50% pain relief. We found a mean gain +0.09 to +0.15 on EQ-5D in utility associated with the remission health state compared to ≥50% pain relief. This gain was both statistically significant and clinically important (i.e., >0.074) (20). The data and HRQoL utility values were derived from studies with ECAP SCS. Future studies of SCS in particular and other chronic pain treatments in general need to evaluate if similar utility gains are obtained for these health states mainly the remission health state.

The health states considered for this study reflect those used in previous economic models to assess the cost-effectiveness of SCS. The mean index score observed at baseline (i.e., 0.33) corresponds to that previously reported for patients with severe chronic pain with neuropathic characteristics (21). The HRQoL utility values for

**Table 3.** Levels of EQ-5D Utility (UK Values) by Health State at 3- and 12-Month Follow-Up.

| | Mean utility score (95% CI) | Comparison of health states | | Mean utility score (95% CI) | Comparison of health states | |
|---|---|---|---|---|---|---|
| | 3-month | Contrasts | *p* value* | 12-months | Contrasts | *p* value* |
| *Overall VAS pain* | | | | | | |
| No pain relief (NPR) | 0.42 (−2.28 to 3.12) | - | - | 0.14 (−1.91 to 2.20) | - | - |
| Suboptimal pain relief (SPR) | 0.50 (0.42–0.58) | NPR vs. SPR | 0.425 | 0.43 (0.31–0.55) | NPR vs. SPR | 0.149 |
| Optimal pain relief (OPR) | 0.63 (0.57–0.68) | SPR vs. OPR | 0.004 | 0.62 (0.57–0.68) | SPR vs. OPR | <0.0001 |
| Remission (R) | 0.77 (0.73–0.80) | OPR vs. R | <0.0001 | 0.73 (0.69–0.77) | OPR vs. R | <0.0001 |
| *Back VAS pain* | | | | | | |
| No pain relief (NPR) | 0.42 (−2.28 to 3.12) | - | - | 0.32 (0.20–0.44) | - | - |
| Suboptimal pain relief (SPR) | 0.52 (0.44–0.59) | NPR vs. SPR | 0.395 | 0.42 (0.32–0.53) | NPR vs. SPR | 0.481 |
| Optimal pain relief (OPR) | 0.62 (0.57–0.68) | SPR vs. OPR | 0.002 | 0.65 (0.60–0.69) | SPR vs. OPR | <0.0001 |
| Remission (R) | 0.77 (0.73–0.80) | OPR vs. R | <0.0001 | 0.74 (0.70–0.78) | OPR vs. R | <0.0001 |
| *Leg VAS pain* | | | | | | |
| No pain relief (NPR) | 0.37 (0.07–0.67) | - | - | 0.08 (−0.25 to 0.41) | - | - |
| Suboptimal pain relief (SPR) | 0.49 (0.35–0.64) | NPR vs. SPR | 0.484 | 0.49 (0.37–0.61) | NPR vs. SPR | <0.001 |
| Optimal pain relief (OPR) | 0.63 (0.57–0.69) | SPR vs. OPR | 0.343 | 0.58 (0.51–0.64) | SPR vs. OPR | <0.0001 |
| Remission (R) | 0.74 (0.70–0.77) | OPR vs. R | <0.003 | 0.72 (0.68–0.76) | OPR vs. R | <0.0001 |

*Adjusted for baseline EQ-5D utility score, age, gender, pain duration, previous back surgery.
CIs, confidence intervals; VAS, visual analog scale.



  

**Table 4.** Levels of EQ-5D Utility (UK Values) at 3- and 12-Month Follow-Up by Pain Relief as a Continuous Variable.

| | Mean change in utility per percent unit of pain relief change | | | | | |
|---|---|---|---|---|---|---|
| | Univariable analysis | | | Multivariable analysis* | | |
| | Mean | 95% CI | *p* value | Mean | 95% CI | *p* value |
| 3-month | | | | | | |
| Overall pain | 0.004 | 0.003–0.005 | <0.0001 | 0.005 | 0.004–0.006 | <0.0001 |
| Back pain | 0.004 | 0.003–0.005 | <0.0001 | 0.004 | 0.003–0.005 | <0.0001 |
| Leg pain | 0.003 | 0.002–0.004 | <0.0001 | 0.003 | 0.002–0.004 | <0.0001 |
| 12-month | | | | | | |
| Overall pain | 0.005 | 0.004–0.006 | <0.0001 | 0.005 | 0.004–0.006 | <0.0001 |
| Back pain | 0.004 | 0.003–0.005 | <0.0001 | 0.004 | 0.003–0.005 | <0.0001 |
| Leg pain | 0.004 | 0.003–0.005 | <0.0001 | 0.004 | 0.003–0.005 | <0.0001 |

*Adjusted for baseline EQ-5D utility score, age, gender, pain duration, previous back surgery.

the optimal pain relief health state observed in this study are in line with previously reported utility values employed in economic models of SCS, that is, 0.60 (22–24). However, the index scores observed in this study for the no pain relief health state ranged from 0.08 (leg VAS pain at 12-month follow-up) to 0.42 (overall and back VAS pain at 3-month follow-up). While the value of 0.08 is in line with index scores previously reported (i.e., 0.17), the value of 0.42 is substantially greater. This variance is likely due to the very limited number of patients (<5%) that did not experience any pain relief in this study as all patients received SCS. Previous assessments of HRQoL associated with health states include patients receiving usual care, hence likely to have a larger proportion of patients with no perceived pain reduction (25).

The mean utility score observed for the remission health state ranged between 0.72 and 0.74 at 12-month follow-up, only slightly lower than the mean utility score of 0.79 reported for a UK general population (21). The proportion of patients reporting ≥80% pain relief at 12-month follow-up ranged from 54% to 62%. Closed-loop SCS was associated with 15–19% higher remission rates compared to open-loop SCS at 3- and 12-month follow-up, respectively (6). The proportion of patients with ≥80% pain relief was first reported in the 2007 PROCESS trial comparing SCS using traditional parameters to conventional medical management where 22% of SCS subjects achieved this level of VAS leg pain relief at 6 months (19). A recent retrospective analysis found 22% of patients with SCS using traditional parameters had >80% pain relief on the Numeric Rating Scale (NRS) at 12-month follow-up (20% of patients with NRS = 0) (15). Another retrospective analysis examined remission defined as a VAS back pain score ≤ 3.0 cm for at least 6 months and reported 55% of patients with high frequency SCS in remission at 24-month follow-up (16). The same study observed that a subject in remission at 12 months was 8.1 times more likely to be in remission at 24 months than a patient who was not (odds ratio = 8.1, 95% CI = 3.7–17.4). As was observed with ECAP SCS in the current study, higher remission rates have been observed with newer SCS models and thus it is important to consider this in economic models of cost effectiveness for these new technologies.

The utility scores for the different health states varied considering the use of EQ-5D UK or US value set. The instrument and value set used to derive utility scores should be clearly reported. As previously reported, the choice between EQ-5D and other HRQoL tools such as the SF-6D can result in large differences in the estimation of utility scores for chronic pain (21). Previous studies have reported differences between EQ-5D specific country tariffs among type 2 diabetes patients (26), Crohn's disease (27), or

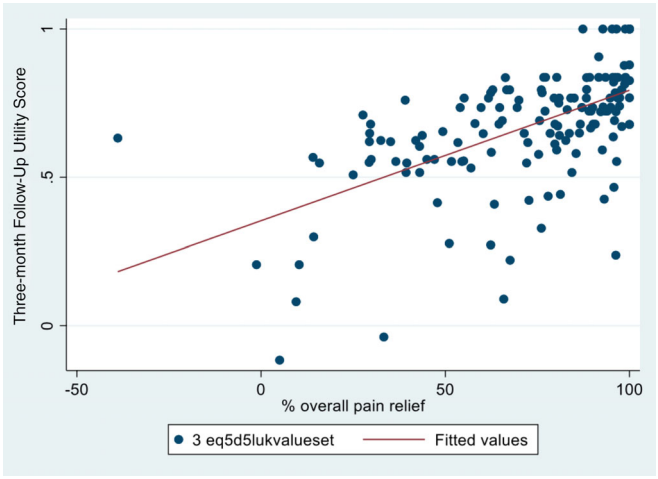


**Figure 2.** Univariable relationship between EQ-5D utility (UK values) at 3-month follow-up versus percent overall pain relief. [Color figure can be viewed at wileyonlinelibrary.com]

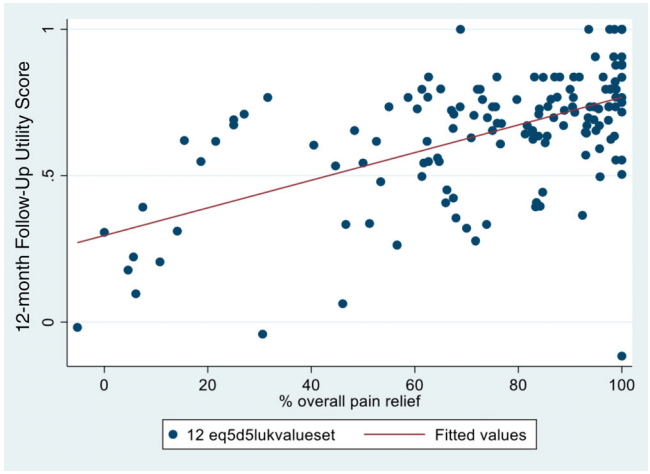


**Figure 3.** Univariable relationship between EQ-5D utility (UK values) at 12-month follow-up versus percent overall pain relief. [Color figure can be viewed at wileyonlinelibrary.com]



  

general population (28) but not for patients with HIV (29). There is evidence that SF-6D preference weights differ between countries. Comparisons between SF-6D value sets for UK and US (30), Hong Kong (31), Japan (32), and Portugal (33) suggest important differences in valuation. Utility scores derived from different instruments or considering different countries preference weights should not be used interchangeably with risk of impacting funding decisions.

It is unclear how the differences between the utility scores derived from EQ-5D value sets would impact an economic evaluation. Since the utility values are applied to both treatments and their comparators, to some extent the differences may be even including the incremental gain associated with an intervention (34). While several model-based economic evaluations of SCS have been published (35), the impact of using different value sets and adding a remission health state needs to be further investigated.

### Strengths and Weaknesses

We believe this to be the first empirical study to analyze and quantify the impact of remission on HRQoL. Analyses conducted considered index scores derived from the EQ-5D employing preference weights for both the UK and US. Our findings were consistent across pain locations and follow-up timings. Our study population is reflective of other trial populations that included people with chronic pain.

However, we recognize that there are potential limitations. First, as this was an observational comparison of utility values across pain relief states, our findings may be subject to confounding and selection bias. However, we sought to minimize such bias by undertaking multivariable analysis adjusting for key patient demographics and baseline utility scores that may differ across health states. Second, the minimally clinical important difference for the EQ-5D has been reported to be 0.074 (20). We used a conservative approach to determine the sample size required for this study by using a difference of 0.1 between pain thresholds; a larger difference than that observed specifically for people with chronic pain with neuropathic characteristics (i.e., 0.09 mean difference between mild and moderate neuropathic pain) (21). Although the number of patients included in the study were sufficient to detect an important difference in HRQoL utility scores, the number of patients with no pain relief were insufficient to produce reliable findings for the no pain relief health state. We would therefore recommend that researchers continue to use existing utility values for the no pain relief state. Third, other definitions of remission have been proposed such as maintenance of a VAS pain score ≤ 3.0 cm for at least 6 months (16). However, in order to inform future economic evaluations of SCS, we specifically choose a definition based on percentage of pain relief as this aligns with the structure of existing models. Finally, the EVOKE and AVALON trials used strict eligibility criteria. It is important to evaluate if the results presented within this study are observed in routine clinical practice.

### Implications for Practice

The findings of this study have important implications for future cost-effectiveness analyses and reporting of clinical trials in the field of chronic pain. Reflective of technological innovations in the therapy, a number of recent SCS clinical trials have reported increased proportion of patients reporting higher rates of pain relief. The EVOKE and AVALON trials (data used in this analysis) have reported 56% and 54%, respectively, of participants with closed-loop therapy experiencing ≥80% pain relief at 12-month follow-up (6,7). Based on our findings, we would recommend that economic models of chronic pain be updated to include the remission health state. By doing so, future economic evaluations will more appropriately capture the health gains and cost-effectiveness of interventions.

Health states based on levels of pain relief also align with IMMPACT recommendations for studies of chronic pain populations to report the proportions of patients achieving moderate clinically important changes (i.e., ≥30%) and substantial clinically important changes (i.e., ≥50%) (36). We propose that future studies also report the proportion of patients in remission, that is, reporting ≥80% pain relief.

In conclusion, this study shows that the improvement in HRQoL utility of people with chronic pain treated with ECAP SCS is directly associated with their level of pain relief. Patients in a remission health state defined as ≥80% pain relief report statistically and clinically significant better HRQoL when compared with more traditional levels of pain relief of ≥50%. Based on our findings, we would recommend that future clinical trials consistently include the reporting of participants who experience ≥80% pain relief and that economic models of chronic pain be updated to include the remission health state.

## Authorship Statement

Rod S. Taylor conceptualized the study. Rui V. Duarte and Rod S. Taylor designed the study. Nicole Soliday and Angela Leitner provided the anonymized individual patient data. Rui V. Duarte and Rod S. Taylor conducted the analysis and interpretation of the data. Rui V. Duarte and Rod S. Taylor wrote the first draft of the manuscript. All authors contributed to drafts of the manuscript and approved the final version of the manuscript.

**How to Cite this Article:**

Duarte R.V., Soliday N., Leitner A., Taylor R.S. 2020. Health-Related Quality of Life Associated With Pain Health States in Spinal Cord Stimulation for Chronic Neuropathic Pain. Neuromodulation 2020; E-pub ahead of print. DOI:10.1111/ner.13267

## REFERENCES

1. Wolowacz SE, Briggs A, Belozeroff V et al. Estimating health-state utility for economic models in clinical studies: an ISPOR good research practices task force report. *Value Health* 2016;19:704–719.
2. Deer T, Slavin KV, Amirdelfan K et al. Success using neuromodulation with BURST (SUNBURST) study: results from a prospective, randomized controlled trial using a novel burst waveform. *Neuromodulation* 2018;21:56–66.
3. Kapural L, Yu C, Doust MW et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology* 2015;123:851–860.
4. Sweet J, Badjatiya A, Tan D, Miller J. Paresthesia-free high-density spinal cord stimulation for postlaminectomy syndrome in a prescreened population: a prospective case series. *Neuromodulation* 2016;19:260–267.
5. Deer TR, Levy RM, Kramer J et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and

  

causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2017;158: 669–681.
6. Mekhail N, Levy RM, Deer TR et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *Lancet Neurol* 2020;19:123–134.
7. Russo M, Brooker C, Cousins MJ et al. Sustained long-term outcomes with closed-loop spinal cord stimulation: 12-month results of the prospective, multicenter, open-label Avalon study. *Neurosurgery* 2020. ; E-pub ahead of print.
8. Levy RM. The need for mechanism-based medicine in neuromodulation. *Neuromodulation* 2012;15:273–279.
9. Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: analysis of technical drawbacks and solutions. *Neurosurgery* 1997; 40:990–996.
10. Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. *Brain Res* 2014;1569:19–31.
11. Parker JL, Karantonis DM, Single PS et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. *Neuromodulation* 2013;16:295–303.
12. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain* 2012;153:593–601.
13. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45–56.
14. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. *Psychol Med* 1988;18:1007–1019.
15. Khan H, Pilitsis JG, Prusik J, Smith H, McCallum SE. Pain remission at one-year follow-up with spinal cord stimulation. *Neuromodulation* 2018;21:101–105.
16. Amirdelfan K, Gliner BE, Kapural L et al. A proposed definition of remission from chronic pain, based on retrospective evaluation of 24-month outcomes with spinal cord stimulation. *Postgrad Med* 2019;131:278–286.
17. Herdman M, Gudex C, Lloyd A et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20: 1727–1736.
18. van Hout B, Janssen MF, Feng YS et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15:708–715.
19. Kumar K, Taylor RS, Jacques L et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132:179–188.
20. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14: 1523–1532.
21. Torrance N, Lawson KD, Afolabi E et al. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? *Pain* 2014;155:1996–2004.
22. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess* 2009;13:iii, ix-x.
23. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. *Clin J Pain* 2010;26:463–469.
24. Annemans L, Van Buyten JP, Smith T, Al-Kaisy A. Cost effectiveness of a novel 10 kHz high-frequency spinal cord stimulation system in patients with failed back surgery syndrome (FBSS). *J Long Term Eff Med Implants* 2014;24:173–183.
25. Manca A, Kumar K, Taylor RS et al. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). *Eur J Pain* 2008;12:1047–1058.
26. Kiadaliri AA, Eliasson B, Gerdtham UG. Does the choice of EQ-5D tariff matter? A comparison of the Swedish EQ-5D-3L index score with UK, US, Germany and Denmark among type 2 diabetes patients. *Health Qual Life Outcomes* 2015;13:145.
27. Mozzi A, Meregaglia M, Lazzaro C, Tornatore V, Belfiglio M, Fattore G. A comparison of EuroQol 5-dimension health-related utilities using Italian, UK, and US preference weights in a patient sample. *Clinicoecon Outcomes Res* 2016;8: 267–274.
28. Gerlinger C, Bamber L, Leverkus F et al. Comparing the EQ-5D-5L utility index based on value sets of different countries: Impact on the interpretation of clinical study results. *BMC Res Notes* 2019;12:18.
29. Huang IC, Willke RJ, Atkinson MJ, Lenderking WR, Frangakis C, Wu AW. US and UK versions of the EQ-5D preference weights: does choice of preference weights make a difference? *Qual Life Res* 2007;16:1065–1072.
30. Craig BM, Pickard AS, Stolk E, Brazier JE. US valuation of the SF-6D. *Med Decis Making* 2013;33:793–803.
31. Kharroubi SA, Brazier JE, McGhee S. A comparison of Hong Kong and United Kingdom SF-6D health states valuations using a nonparametric Bayesian method. *Value Health* 2014;17:397–405.
32. Kharroubi SA. A comparison of Japan and U.K. SF-6D health-state valuations using a non-parametric Bayesian method. *Appl Health Econ Health Policy* 2015; 13:409–420.
33. Ferreira LN, Ferreira PL, Rowen D, Brazier JE. Do Portuguese and UK health state values differ across valuation methods? *Qual Life Res* 2011;20:609–619.
34. Mulhern B, Feng Y, Shah K et al. Comparing the UKEQ-5D-3L and English EQ-5D-5L value sets. *Pharmacoeconomics* 2018;36:699–713.
35. Niyomsri S, Duarte RV, Eldabe S et al. A systematic review of economic evaluations reporting the cost-effectiveness of spinal cord stimulation. *Value Health* 2020;23:656–665.
36. Dworkin RH, Turk DC, Wyrwich KW et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105–121.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

## COMMENTS

This is an interesting piece of work that clearly demonstrates the link between improvements in Health-related Quality of Life (HRQoL) and its association with the level of pain relief. These facts will be of interest to patients healthcare, commissioners and clinicians alike.

Sam Eldabe, MBBS
*Middlesbrough, United Kingdom*

***

This manuscript uses the combined population of subjects recruited to two clinical trials in Australia and USA and looks at the relationship between responder rates as judged by pain score percentage change with that of the EQ5D-5L, a measure of Health related quality of life. We are used to looking at responder rates of 30 or 50% pain reduction but since more than half of the subjects treated in these trials achieved 80% reduction, it is important to see if the correlation between responder rate and utility score continues. The authors opine that future studies should report those patients with greater than 80% pain reduction and that economic models providing the cost effectiveness data be upgraded. The added utility score difference can have a profound influence on the cost effectiveness of the newer generation of SCS therapies.

Simon Thomson, MBBS
*Basildon, Essex United Kingdom*

***

The result of this study is not surprising to me - more pain relief leads to more quality of life improvement. Intrinsically, this seems likely to me until such time as the quality of life has approximated the normal population. I am unsure at this time what is the best definition of remission/remitter status. Is it VAS<3 as promoted by Amirdelfan et al., or is it >80% pain reduction from baseline? I think the jury is out on that one and we need more nuanced studies to answer that question. Probably both are valid if I have a stab at it.

Figure 3 is instructional. Setting aside one outlier at 30% pain relief, one needs a minimum of 60% pain relief to see a Utility Score of 0.75 or greater. It is not all about percentage pain relief - 2/3rds of the remission (>80% pain relief) group had a Utility Score less than 0.75. So more factors are at play here. I would posit that extended walking distance, full wean from opioids and minimal device interaction/attention time are additional factors that play into a very high quality of life outcome. I believe we need to understand the significant components that go into a high quality of life score and then tune our therapies to deliver those outcomes. Only then can we say we have truly gone beyond the VAS in our delivery of care. This is not a dry, dusty and pointless field of esoteric research. It is a rich vein of understanding



  

how we can connect meaningfully with our patients and improve their lives holistically. I echo the authors' call for additional outcome states to be added to the literature above and beyond >50% pain relief.

Marc Russo, MBBS
*Broadmeadow, NSW Australia*

***

This study used data of  patients from two previously reported studies in patients with back and leg pain who received an ECAP SCS system. The study demonstrated that patients in a remission state (pain relief >80%) reported statistically and clinically significant better health-related quality of life (HRQoL).

Michael E. Harned, MD
*Lexington, KY USA*



  