Biomarkers and Health-Related Quality of Life in End-Stage Renal Disease: A Systematic Review

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Background and objectives: Health-related quality of life (HRQOL) predicts mortality in ESRD, yet adoption of HRQOL monitoring is not widespread, and regulatory authorities remain predominantly concerned with monitoring traditional biologic parameters. To assist with future efforts to adopt HRQOL monitoring while acknowledging the importance of biomarkers, this study sought to establish which domains of HRQOL are most affected by ESRD and to measure the strength of evidence linking common biomarkers to HRQOL in ESRD.

Design, setting, participants, & measurements: A systematic review was performed to identify studies that measured HRQOL in ESRD. Data were abstracted according to a conceptual model regarding the measurement of HRQOL differences, and HRQOL data were converted to weighted mean effect sizes and correlation coefficients.

Results: The impact of ESRD was largest in the Short Form 36 domains of physical functioning (e.g., role-physical, vitality) and smallest in mental functioning (e.g., mental health, role-emotional). Dialysis adequacy, as measured by Kt/V, was a poor correlate for Short Form 36 scores. Similarly, mineral metabolism (e.g., calcium × phosphorous, parathyroid hormone) and inflammatory (e.g., C-reactive protein, TNF) biomarkers had small effect sizes and correlations with HRQOL. In contrast, hematocrit demonstrated small to moderate relationships with mental and physical HRQOL, and nutritional biomarkers (e.g., albumin, creatinine, body mass index) demonstrated moderate to large relationships.

Conclusions: HRQOL in ESRD is most affected in the physical domains, and nutritional biomarkers are most closely associated with these domains. In contrast, Kt/V, mineral metabolism indices, and inflammatory markers are poor HRQOL correlates.

likely underestimates the true burden of illness engendered by ESRD.

In light of the disconnect between the growing importance of measuring HRQOL in ESRD and the continued emphasis on tracking biomarkers as the predominant determinant of quality care, it is important to understand the strength of evidence linking individual biomarkers to HRQOL. This is important because HRQOL remains a robust predictor of morbidity and mortality in ESRD and is an important surrogate of quality care (8,11–14). Thus, knowing which biomarkers optimally predict HRQOL may provide insight into how best to manage ESRD. We, therefore, performed a systematic review first to establish which domains of HRQOL are most affected by ESRD in general and then to establish the strength of evidence linking common biomarkers to individual HRQOL domains in ESRD.

Materials and Methods

Systematic Review

We performed a systematic review of MEDLINE to identify relevant English-language publications from 1990 through 2007. We sought two types of studies: (1) Studies that compared HRQOL data between patients with ESRD and non-ESRD control subjects and (2) studies that assessed variations in HRQOL across biomarkers. Refer to the Technical Appendix for a detailed description of our systematic review method.

Conceptual Framework Overview

The most clinically meaningful method of measuring HRQOL differences between groups is to anchor data to relevant clinical outcomes (16), such as biomarkers. We performed our analyses according to this conceptual framework—a method we have used in other areas of medicine (17). HRQOL differences between groups can be measured using a scaled effect size (ES). The ES for between-group HRQOL differences is calculated using the following equation:

\[
ES = \frac{\text{HRQOL}_{\text{group1}} - \text{HRQOL}_{\text{group2}}}{\text{SD}_{\text{group1}}}
\]

Cohen has standardized the interpretation of the ES as follows: <0.2 is a small clinical effect, 0.5 is a moderate effect, and >0.8 is a large effect (18). The advantage of this interpretation scheme is that HRQOL outcomes in different interventions and diseases can be compared using a standardized ES, a statistic with clinical relevance that serves as an “exchange currency” across disparate fields in medicine.

Statistical Analysis

We converted HRQOL data from each study to ES data and adopted absolute values for our pooled estimates. We then calculated the weighted mean for each relevant statistic stratified by “high” versus “low” levels of each biomarker, as defined by the literature. When available, we abstracted adjusted HRQOL differences in lieu of unadjusted data. In instances in which a clinically interpretable statistic could not be calculated from the available data, we sought data regarding correlations (i.e., Pearson correlation coefficient \(r\) values) between HRQOL and individual parameters. For parameters with two or more studies with common correlations, we calculated the sample size-weighted pooled \(r\) value using the weighted mean as our point estimate and calculated 95% confidence intervals (CI) around the point estimate, a technique used by previous investigators linking outcomes to HRQOL in ESRD (19).

Results

Study Selection

The search strategy identified 2335 titles. Of these, we selected 47 studies that met our explicit inclusion criteria (inter-observer agreement was high \(K >0.9\) for each phase of selection).

HRQOL in ESRD versus Healthy Control Subjects

We identified 20 studies that compared HRQOL in patients who had ESRD and were on dialysis with healthy control subjects (Table 1) (11,14,20–37). All 20 studies measured HRQOL with the Short Form-36 Health Survey (SF-36), the most widely used and validated measure of HRQOL in the nephrology literature (38). Eighteen studies provided data to calculate an ES for HRQOL in ESRD versus healthy non-ESRD control subjects (Table 1) (11,14,20–29,31–35,37). The largest ES for ESRD was in the physical function (weighted ES 1.4) and general health (1.2) scales, followed by the role-physical (1.0) and vitality (0.73) scales. Ten studies measured ES in the physical component score (PCS) and mental component score (MCS) (11,20–22,26–28,31,32). The weighted mean estimates were 1.2 and 0.4 for PCS and MCS, respectively.

Results Stratified by Traditional Biomarkers

Dialysis Adequacy

We identified 19 studies that included more than 1500 patients and measured HRQOL stratified by Kt/V (13,22,27,32,33,35,36,38–49).

(a) Effect Sizes.

The largest HRQOL ES for Kt/V was registered in the bodily pain and vitality scales of the SF-36 (Table 2). The ES across all other scales was ≤0.2, indicating that Kt/V had a small relationship with HRQOL. Two studies measured the relationship between Kt/V and both PCS and MCS, and the relationship with Kt/V and these domains was small (ES ≤0.1 for both) (46,47). Two studies presented data using the disease-targeted Kidney Disease Quality of Life (KDQOL) instrument, a questionnaire that includes the SF-36 as a generic core surrounded by disease-specific scales (46,48). The ES was ≤0.2 for all disease-targeted HRQOL scales (46,48).

(b) Correlation Coefficients.

We identified 48 analyses, within 14 studies, that measured the correlation between Kt/V and SF-36 scale scores (13,22,27,32,33,35,39–45). The weighted mean \(r\) value between Kt/V and SF-36 scores was 0.1 (95% CI 0.02 to 0.22), a NS relationship. In contrast, Korevaar et al. (50) found significant correlations between Kt/V and several scales of the KDQOL, including the symptom scale \(r = 0.23\), effects of kidney disease scale (0.27), burden of kidney disease scale (0.36), work status scale (0.31), and cognitive function scale (0.22). There was no significant relationship between Kt/V and social, sexual, or sleep function on the KDQOL (50).

Anemia

There are extensive data linking anemia to mortality and HRQOL decrements in hemodialysis (51–59). We identified 21 studies that includes more than 2000 patients and measured the relationship between hematocrit (Hct) levels and HRQOL (13,22,27,30–32,35,39,43,45,59–68).

(a) Effect Sizes.

Four studies provided HRQOL ES data using the SF-36 instrument (65–68). Hct had the largest HRQOL
Table 1. Studies comparing HRQOL in patients with ESRD versus healthy control subjects: Cross-sectional ES between groups

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>No. of Patients with ESRD</th>
<th>SF-36 Scales</th>
<th>Physical Function</th>
<th>Role-Physical</th>
<th>Bodily Pain</th>
<th>General Health</th>
<th>Vitality</th>
<th>Social Function</th>
<th>Role-Emotional</th>
<th>Mental Health</th>
<th>PCS</th>
<th>MCS</th>
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<td>0.62</td>
<td>0.31</td>
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</table>

aData are presented across the eight Short Form-36 Health Survey (SF-36) scales and the two SF-36 component scales. The weighted mean and median are presented for the cumulative data (bottom two rows). For example, patients with ESRD score, on average, 1.4 SD lower on the physical function scale versus healthy control subjects (effect size [ES] 1.4). All results are expressed as absolute values. HRQOL, health-related quality of life; MCS, Mental Component Score; PCS, Physical Component Score.
Table 2. Summary results of HRQOL data by biomarker

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>No. of Studies</th>
<th>No. of Patients with ESRD</th>
<th>SF-36 Scales</th>
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<th>MCS</th>
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<tr>
<td>ES Data</td>
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<tr>
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<td>0.12</td>
<td>0.01</td>
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<tr>
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<td>0.23</td>
<td>0.22</td>
<td>0.25</td>
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<tr>
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<td>0.80</td>
<td>0.40</td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
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<td>–</td>
<td>0.10</td>
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<td>54</td>
<td>0.14</td>
<td>–</td>
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</tr>
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</table>

aData are presented across the eight SF-36 scales and the two SF-36 component scales. The top of the table presents results expressed as weighted mean ES (expressed as absolute values), and the bottom presents weighted mean correlation coefficients (r values). Refer to the text for details. BMI, body mass index; Ca × P, calcium-phosphorus product; PTH, parathyroid hormone; CRP, C-reactive protein.
ES relationship with the mental health scale (ES 0.33), followed by the role-physical (0.24) and bodily pain/physical function (both 0.23) scales. The ES across all other scales was ≤ 0.2 (Table 2).

(b) Correlation Coefficients. We identified 74 analyses, contained within 16 studies, that measured the correlation between Hct and SF-36 scale scores (13,22,27,30,31,35,36,39,43,45,59,61–64). The weighted mean r value between Hct and SF-36 scale scores was 0.15 (95% CI 0.13 to 0.17). The largest weighted mean correlations were recorded in the physical function, vitality, and physical component scores. We identified two studies that measured the correlations between Hct and KDQOL scores (9,29). Vazquez et al. (9) found that Hct correlated significantly with patient satisfaction, effects of kidney disease, and quality of social interaction scales of the KDQOL; however, Hct did not significantly correlate with the cognitive function, sexual function, sleep, social support, symptom, or burden of kidney disease scales (9). In contrast, Carmichael et al. (29) found a statistically significant adjusted correlation between Hct and the quality of social interaction scale of the KDQOL (r = 0.21) but no significant correlations with any other disease-targeted scales.

Nutritional Biomarkers. Of the commonly measured nutritional and anthropomorphic biomarkers in ESRD, serum albumin, serum creatinine, and body mass index (BMI) have the most data linking each to HRQOL.

(a) Serum Albumin. We identified 17 studies that included more than 4000 patients and measured the relationship between serum albumin levels and HRQOL in ESRD (10,13,21,22,26,27,30,32,36,39,40,43,45,59,69–71).

1. Effect Sizes. We identified only one study that provided HRQOL ES data stratified by serum albumin. Allen et al. (26) documented moderate to large ES of albumin in the PCS (ES 0.8) and MCS (ES 0.4) when dichotomizing albumin as <3.5 versus >3.5 g/dl.

2. Correlation Coefficients. We identified 59 analyses, contained within 16 studies, that measured the correlation between serum albumin and SF-36 scale scores (13,21,22,26,27,30,32,36,39,40,43,45,59,69–71). The weighted mean r value between albumin and SF-36 scale scores was 0.15 (95% CI 0.05 to 0.25). The largest weighted mean correlations were recorded in the physical function, mental health, and PCS (Table 2). Kurella et al. (10) provided further data correlating albumin with disease-targeted HRQOL, using the KDQOL cognitive function subscale as their outcome. The authors documented a highly significant adjusted correlation between albumin and the KDQOL subscale (r = 0.30; P = 0.007).

(b) Serum Creatinine. Allen et al. (26) measured ES data stratified by low (<83 mg/L) versus high (≥122 mg/L) serum creatinine levels in a cross-sectional analysis of 1545 dialysis patients enrolled in the Hemodialysis (HEMO) study. The authors found that patients with low creatinine had a significantly lower adjusted SF-36 PCS score versus patients with higher levels (ES 2.0). In contrast, the relationship between creatinine and MCS was NS. We identified six studies that measured correlation coefficients for the relationship between creatinine and SF-36 scores in ESRD (13,31,40,61,72,73). The weighted mean r value between creatinine and SF-36 scale scores was 0.29 (95% CI 0.21 to 0.37). The largest correlations were recorded in the general health, mental health, and bodily pain scales (Table 2).

(c) Body Mass Index. We identified four studies that measured the relationship between BMI and HRQOL in ESRD (36,45,73,74). In a cross-sectional study of 65 patients with ESRD, Kalantar-Zadeh et al. (73) documented highly significant independent correlations between BMI and both PCS (r = −0.35) and MCS (r = −0.31) scores of the SF-36 after adjusting for potential confounders. Similarly, in a study of 75 dialysis patients, Goller et al. (36) found a significant relationship between BMI and SF-36 physical function scores. Kusek et al. (74) documented a significant relationship with PCS but not MCS. In contrast, Mingardi et al. (45) were unable to document significant relationships between BMI and any SF-36 domains.

Mineral Metabolism Biomarkers

Calcium-Phosphorous Product and Serum Calcium. We identified one study that linked calcium-phosphorous product (Ca × P) to HRQOL data (75). In a cross-sectional survey of more than 4000 patients with ESRD in Japan, Tanaka et al. (75) found no significant difference in mental health scores between patients with low (<42) versus high (≥62) Ca × P. When treated as a linear variable, there was no significant correlation between Ca × P and SF-36 mental health scores. The same authors measured the relationship between serum corrected calcium levels and HRQOL and found that patients with high (>11) versus low (<8.4) calcium had a statistically significant difference in SF-36 mental scale scores (ES 0.22).

Parathyroid Hormone Levels. We found four studies that measured the relationship between parathyroid hormone (PTH) and SF-36 scores in ESRD (13,45,75,76). Tanaka et al. (75) found a NS difference in mental health scores in patients with high (>600) versus low (<150) PTH levels (ES 0.1). When treated as a linear variable, PTH remained unable to predict independently SF-36 MCS or PCS scores in both a cross-sectional survey of 65 patients with ESRD in the United Kingdom and a survey of 497 patients in Taiwan (13). Similarly, Mingardi et al. (45) found that PTH did not significantly correlate with any of the SF-36 scale scores. Using the KDQOL, Klersy et al. (76) found no significant relationship between PTH and any disease-targeted HRQOL domains.

Inflammation Biomarkers

C-Reactive Protein. We identified five analyses, contained within three studies (13,73,77), that measured the correlation between C-reactive protein (CRP) levels and SF-36 scale scores. None of the five identified analyses revealed significant correlations between CRP and any SF-36 scale.

TNF and IL-1. We found one study that measured the relationship between either TNF or IL-1 and the SF-36 scores (77). In a cross-sectional analysis of 54 dialysis patients, Hung et al. (77) found a NS correlation between TNF and the SF-36 phys-
Discussion

Although monitoring biomarkers is central to the successful treatment of patients with ESRD, it is necessary but insufficient to understand fully patients’ overall burden of illness. Data indicate that HRQOL is a consistent and powerful predictor of overall mortality in ESRD, on par with the predictive ability of traditional biomarkers such as Kt/V (14). Thus, it is important to complement biologic data with information about patients’ overall HRQOL, yet, with few exceptions (78), adoption of routine HRQOL monitoring in everyday clinical practice remains suboptimal. In the absence of widespread efforts to track HRQOL, an important first step is to measure formally the relationship between common biomarkers and HRQOL. We conducted this systematic review first to establish which domains of HRQOL are most affected by ESRD in general and then to pool data to measure the magnitude of relationships between traditional biomarkers, including those supported by Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and tracked by Medicare, and patient-reported HRQOL.

Our study has several key findings. First, patients with ESRD have consistently diminished HRQOL compared with matched control subjects without ESRD. Specifically, the HRQOL decrement in ESRD is most pronounced in physical function and vitality. In contrast, the impact of ESRD is least pronounced in mental health. This suggests that compared with interventions directed at improving physical HRQOL in ESRD, efforts aimed at improving mental HRQOL may be limited by a “ceiling effect,” because there is relatively less room for improvement in the mental versus physical domains of HRQOL in ESRD.

Second, we found that dialysis adequacy, although a strong predictor of mortality in ESRD, is a poor predictor of HRQOL. Specifically, the pooled ES of high versus low Kt/V is <0.2 SD, a small clinical effect (18). The pooled r value of 0.1 also suggests that Kt/V has a minimal relationship with HRQOL. These findings indicate that Kt/V fails to capture key aspects of illness related to ESRD and is a poor correlate for HRQOL.

Third, mineral metabolism biomarkers, including PTH, Ca × P, and serum calcium, have no significant relationship to HRQOL. As with Kt/V, these data indicate that mineral metabolism markers may not reliably track with the patient-reported experience of the illness. Given the consistency of evidence, it is reasonable to conclude that intervening on mineral metabolism biomarkers through therapeutic or dietary maneuvers, although important for other purposes, may not have a meaningful impact on patient-reported HRQOL; however, it is possible that a more specific HRQOL questionnaire might better capture the impact of these physiologic perturbations. Investigators studying the relationship between mineral metabolism and HRQOL might benefit from developing such a disease-targeted instrument.

Fourth, although data indicate that inflammatory markers, such as TNF, CRP, and IL-1, are consistent predictors of mortality in ESRD, their relationship to HRQOL seems minimal. This emphasizes that the mechanisms that lead to poor HRQOL may be parallel to but are different from the mechanisms that contribute to mortality in ESRD; however, our review found relatively few data linking inflammatory markers to HRQOL, suggesting that further research is necessary before making any definitive conclusions about the contributing role of inflammation to HRQOL decrements in ESRD.

Fifth, the data indicate that Hct has a small to moderate but consistent relationship with HRQOL in ESRD. When treated as a linear variable, Hct is most highly correlated with the physical function and vitality domains of the SF-36, the same domains most affected by ESRD in general (Table 1). This alignment of Hct with key HRQOL domains in ESRD is supported by data that correcting anemia can improve HRQOL, through both pharmacologic (19) and nonpharmacologic interventions. As an example of the latter, Hamilton and Hawley (79) demonstrated that HRQOL was improved for patients who had ESRD and were exposed to a nurse-run outpatient anemia management program compared with patients who received usual care; however, it must be emphasized that the relationship between Hct and HRQOL remains modest (pooled r = 0.15; ES range 0.1 to 0.34), suggesting that knowing patients’ Hct is necessary—but by no means sufficient—to capture fully overall HRQOL.

Last, our review reveals that nutritional biomarkers in ESRD, including albumin, creatinine, and BMI, are moderate to large predictors of both generic and disease-targeted HRQOL in ESRD. The impact of nutritional indices spans all physical and mental HRQOL domains, with particularly large ES in the physical component score of the SF-36. These results are important because nutritional markers are potentially modifiable and, in some instances, can be intervened on with both pharmacologic and nonpharmacologic therapies. This is supported by data indicating that directed nutritional and exercise programs can improve HRQOL for dialysis patients (66). Coupled with data that nutritional indices are among the strongest predictors of overall mortality in ESRD (80), these results emphasize that nutritional biomarkers are central to dictating both morbidity and mortality. A practical implication of these findings is that poor nutritional status should prompt a formal HRQOL assessment in affected patients, and this information should be recorded and tracked as part of everyday care to optimize treatment in these high-risk patients.

Our review has several limitations. First, we combined studies of different design, follow-up, sample size, population characteristics, and case-mix adjustment. This heterogeneity precludes any ability to perform a meta-analysis and tends to undermine any “cut-and-dry” conclusions about strict rank ordering of biomarkers. We did attempt to acknowledge heterogeneity between studies by calculating sample size-weighted means for all of our pooled estimates, a maneuver that accounts for the expectation that larger studies are theoretically more precise than smaller studies. Second, our analysis did not target other factors that may predict HRQOL in ESRD, including psychosocial variables (e.g., marital status, employment status [30,35,81]), dialysis practice variables (e.g., type and timing of dialysis [82,83]), individual comorbidities (47,84) and symptoms (e.g., poor appetite [47], insomnia), and structure/
process characteristics (e.g., availability of exercise programs [66,85], use of predialysis clinics [86]), among others. These factors undoubtedly have a major impact on outcomes in dialysis; however, expanding our analysis to this range of factors is beyond the scope of our more modest exercise, which is to focus explicitly on the predictive role of biomarkers in ESRD. Third, our review did not find data regarding nonlinear relationships between biomarkers and HRQOL. Data indicate that several biomarkers in dialysis have curvilinear relationships with survival (e.g., PTH, BMI, Ca × P), but it remains unknown whether that relationship extends to HRQOL. Future research should aim to describe better the potential curvilinear relationships between dialysis biomarkers and HRQOL.

Conclusions

Because there is a close connection between HRQOL, morbidity, and mortality in patients with ESRD, it is important to explore which dimensions of HRQOL are most affected by ESRD and to understand how best to monitor HRQOL in individual patients. Our analysis indicates that HRQOL in ESRD is most affected in the physical domains and that nutritional biomarkers and Hct are most closely associated with these domains. In contrast, Kt/V, mineral metabolism indices, and inflammatory markers are poor correlates for HRQOL. These data suggest that, of the commonly measured biomarkers, intervening on nutritional indices, in particular, may have the best impact on overall HRQOL; however, because this conclusion is based on cross-sectional data, future research should prospectively track changes in HRQOL against longitudinal changes in key biochemical indices.

Technical Appendix

Systematic Review Method

We performed a systematic review of MEDLINE and EMBASE to identify English-language publications from January 1990 through September 2007. In addition, we reviewed the bibliographies of key review articles for references not captured by our search strategy. Three reviewers (B.M.R.S., G.M., and E.E.) assessed the generated titles for relevance and rejected by our search strategy. Three reviewers (B.M.R.S., G.M., and E.E.) performed independent abstractions of the resulting articles and entered the data onto a standardized abstraction form. Because most all of the HRQOL data in chronic kidney disease are measured using either the SF-36 or the disease-targeted KDQOL instruments, we focused our review on studies that used these instruments. Other instruments are scattered throughout the chronic kidney disease literature but are not validated in the same way as the SF-36 or KDQOL. Moreover, studies with these alternative instruments are few and far between, making it very difficult to pool data across biomarkers using atypical instruments. Thus, we focused on the bulk of data that arose from the two most common instruments.

Overview of SF-36 Health Survey

The SF-36 instrument is organized into eight discrete scales (physical functioning, physical role limitations, emotional role limitations, bodily pain, general health, emotional well-being, energy/fatigue, and social functioning), which are compiled into two summary scores: (1) Physical component score and (2) mental component score. Each raw scale score is linearly transformed to a 0 to 100 scale using the following formula, with higher scores indicating better HRQOL:

\[
\text{Normalized Raw Score} = \frac{\text{raw scale score} - \text{lowest possible score}}{\text{raw scale range}} \times 100
\]

All eight scales are scored using this same generic equation, and all are scored on a 100-point scale; therefore, all scales are proportionate with regard to interpreting changes on a scale. In other words, a change of 4.2 points on the role-physical scale is proportionately the same as a change in 4.2 points on the vitality scale, because both scales have a 100-point range; however, interpreting score differences across scales is complicated by the fact that each scale has a unique SD. In other words, a difference of 4.2 points on a scale with a wide SD may be less significant than the same difference on a scale with a narrow SD. This is precisely why the ES is used, because the ES anchors the point change on any particular scale by the SD of the scale.

Acknowledgments

B.M.R.S. is supported by VA HSR&D Research Career Development Award RCD 03 to 179-2 and by the CURE Research Center (NIH 2P30 DK 041301-17). Additional support for this study was provided by an investigator-initiated research grant from Amgen, Inc.

The principal investigator, B.M.R.S., maintained full control over all aspects of the study design, implementation, data collection, data analysis, data interpretation, and manuscript preparation and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The contributions of individual authors is as follows:

B.M.R.S. was responsible for study design, study implementation, data collection, data analysis, data interpretation, manuscript preparation, and manuscript approval and is guarantor of article; G.M. was responsible for data collection and manuscript approval; S.R. was responsible for study design, data analysis, data interpretation, and manuscript approval; and E.E. was responsible for study design, study implementation, data collection, and manuscript approval.
Disclosures
S.R. is an employee of Amgen, Inc.

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