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Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa

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Abstract

Health-related quality of life (HrQOL) assessments are gaining importance as outcome measures in cancer clinical trials. A recently published clinical trial reported statistically significant ($P<0.001$) increases in haemoglobin (Hb) levels and significantly ($P<0.01$) increased HrQOL scores following the administration of recombinant human erythropoietin (r-HuEPO, epoetin alfa) versus placebo to anaemic cancer patients who received non-platinum chemotherapy. This study employed five cancer-specific HrQOL instruments. Hb and HrQOL data from this trial were analysed to estimate the minimally important difference (MID) in HrQOL measures that could be interpreted as clinically meaningful, with Hb level selected as the best external standard. Patients were assigned to two groups: improved (Hb increases of $\geqslant 1$ g/dL) or stable (change in Hb of-1 g/dL to <1 g/dL). The MID was first determined as the difference between the mean changes in HrQOL in the improved group versus the stable group. By this analysis, the differences in HrQOL scores between the epoetin alfa group and the placebo group were clinically important for all Hb-sensitive, cancer-specific HrQOL evaluations. Linear regression analyses performed to provide estimates of the MID for specific values of Hb change confirmed that the differences in HrQOL scores between patient groups were clinically significant. These analyses were repeated using a data set from a separate clinical trial, which further supported the conclusion that observed HrQOL changes demonstrated in the multicentre, double-blind study were clinically important. These methods provide one means for interpreting the clinical relevance of changes in HrQOL evaluated in clinical trials.

Keywords: Quality of life; Anaemia; Chemotherapy; Haemoglobin; Cancer

1. Introduction

Health-related quality of life (HrQOL) assessments have become common as outcome measures in cancer clinical trials [1–3], and a number of previously validated instruments are available to assess HrQOL in cancer patients [4]. This trend signifies a widespread recognition that cancer patients face important changes in physical, psychological, and social functioning, overall well-being, and life satisfaction as a consequence of their disease and its treatments [2,5]. As a component of a clinical trial, the statistical significance of changes in HrQOL can be estimated using available analytical methods. There remains a need, however, to interpret the observed numerical differences from HrQOL instruments used in clinical trials in terms that have meaning to clinicians, administrators and patients. Better interpretation of HrQOL results from clinical trials would enable physicians to incorporate those results into their practices including standards of care [6]. More explicitly, there is a need to determine the minimally

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important difference (MID) in a HrQOL measure that will translate into a clinically meaningful outcome [1,7–10].

One factor known to contribute to diminished HrQOL in cancer patients is fatigue, which is often a symptom of anaemia [5,11–14]. Fatigue and its sequelae, including loss of energy, restrictions in the ability to do daily activities, dizziness, and impaired cognitive function, are among the most frequently reported complaints of cancer patients arising from the disease, its treatment, or both [5,11–16]. In a recent survey, the majority of cancer patients with a history of chemotherapy ranked fatigue as the side effect with the greatest impact on daily living [16]. The adverse effects of fatigue have been shown to involve many aspects of patients' quality of life, including relationships with friends and family and the employment status of both patients and caregivers [15,16].

Hb levels, anaemia, and the symptomatic effects of anaemia correlate closely with HrQOL domains [10], and increases in Hb have been associated with increases in HrQOL in several trials [17–20]. Results from clinical studies have shown that recombinant human erythropoietin (r-HuEPO, epoetin alfa; epoetin alfa marketed as EPREX®/ERYPO®, Ortho Biotech, a division of Janssen-Cilag in Europe) can increase haemoglobin (Hb), reduce transfusion requirements, and improve HrQOL in patients, especially for cancer-specific domains such as fatigue, energy level and well-being [17–22].

Full results from a recent multinational, double-blind, placebo-controlled, randomised trial that investigated the effects of epoetin alfa in anaemic cancer patients ($N = 375$) who received non-platinum chemotherapy for non-myeloid malignancies have been previously published [19]. All patients gave written informed consent before study entry, and the study protocol and amendments were reviewed by an independent ethics committee. Mean Hb was significantly ($P < 0.001$) increased in patients who received epoetin alfa (2.2 g/dL) compared with patients who received placebo (0.5 g/dL). Of interest to the current report are the observed effects of increased Hb on HrQOL. Changes in HrQOL for patients who received epoetin alfa or placebo were evaluated by the Functional Assessment of Cancer Therapy-General (FACT-G Total); fatigue subscale (FACT-An Fatigue subscale) of the FACT-Anemia scale (FACT-An); and Cancer Linear Analog Scale (CLAS, also known as the Linear Analog Scale Assessment, or LASA) for energy, ability to do daily activities, and overall QOL. The Medical Outcomes Study Short-Form 36 (SF-36) was also included as a generic HrQOL instrument and was scored into the Physical Component Summary (PCS) and Mental Component Summary (MCS). Statistically significant differences favouring epoetin alfa over placebo were seen for all primary cancer-specific HrQOL assessments by univariate analysis (range, $P = 0.0007$ to $P = 0.0048$, adjusted for multiple comparisons). For the two general scales (SF-36 PCS and MCS), differences in mean scores revealed trends favouring epoetin alfa and determined that no decrement in HrQOL was attributable to treatment [19].

Multiple linear regression analysis showed a significant ($P < 0.05$) advantage for epoetin alfa over placebo for all five Hb-sensitive, cancer-specific scales adjusting for disease progression and other possible confounding variables, and confirmed the results of the univariate analysis [23]. Additionally, statistical significance ($P < 0.05$) was shown for both cross-sectional correlation analysis between Hb and HrQOL for six of seven primary endpoints and for longitudinal analysis between Hb and all seven HrQOL scales (Table 1). The longitudinal correlation between Hb and HrQOL was assessed by deriving the Pearson correlation coefficient between the change in Hb and the change in HrQOL.

Additional analyses of these data were conducted to explore the clinical importance of the observed treatment effect of epoetin alfa on HrQOL. Results of these analyses are presented in this report.

2. Patients and methods

2.1. Determining the minimally important difference

Because Hb is the biomarker most often employed to evaluate anaemia [24], it was selected as the external criterion most appropriate for interpretation of HrQOL changes associated with epoetin alfa. For this analysis, an Hb increase of 1 g/dL, which represents the clinical response that can be expected from transfusion of 1 unit of packed red blood cells, was considered to be the minimally important clinical change by which to evaluate HrQOL results [24–26].

Table 1
Longitudinal correlation analyses between haemoglobin and HrQOL

HrQOL scales	*n*	Correlation coefficient	*P* value	*P* value (adjusted[a])
FACT-G Total	266	0.26	<0.01	<0.01
FACT-An Fatigue subscale	273	0.29	<0.01	<0.01
CLAS: energy	322	0.30	<0.01	<0.01
CLAS: daily activities	322	0.34	<0.01	<0.01
CLAS: overall QOL	321	0.33	<0.01	<0.01
SF-36: physical summary	250	0.26	<0.01	<0.01
SF-36: mental summary	250	0.14	0.03	0.03

HrQOL, health-related quality of life; FACT-G Total, Functional Assessment of Cancer Therapy-General; CLAS, Cancer Linear Analog Scale (also known as Linear Analog Scale Assessment, or LASA); SF-36, Short-Form 36.

[a] Adjusted for multiple comparisons using the sequentially rejective Bonferroni procedure.

Patients were pooled across treatment groups and then most patients were assigned to one of two groups based upon changes in Hb level. 'Improved' patients were defined as those who experienced an increase in Hb of at least 1 g/dL. 'Stable', or unchanged, patients had a change in Hb of less than 1 g/dL to a lower limit of −1 g/dL. The difference in the mean HrQOL change score between the improved and stable groups is the MID for that particular HrQOL measure. Thus: MID = Mean HrQOL Change in Improved Group minus Mean HrQOL Change in Stable Group. The value of the MID for that HrQOL measure is then compared with the observed difference in that measure's change between the epoetin alfa and the placebo group. If the observed difference between treatment groups is greater than or equal to the MID, then that difference may be considered clinically important.

2.2. Linear regression analysis

In the MID derivation outlined directly above, patients who achieved the minimal improvement in Hb included those with Hb increases of at least 1 g/dL. This analysis was conducted on the premise that a 1 g/dL improvement in Hb would result in a clinically meaningful improvement in HrQOL. The actual difference in mean Hb change between the improved and stable groups in the clinical trial was approximately 2.8 g/dL. Thus, the above calculations may lead to an overestimate of the HrQOL MID because they include patients who had greater than 1 g/dL improvements in Hb, which would result in greater HrQOL improvements. Therefore, an alternative method for calculating MID values was adopted that was not subject to this limitation. This involved regressing the change in Hb on the change in HrQOL. Unlike the derivation of MIDs from the difference in mean HrQOL change between stable and improved patients, the derivation of MIDs from regression analyses includes all patients (pooled across treatment groups) and does not ignore patients who experienced declining Hb levels. According to this model, change in HrQOL is the dependent variable, and change in Hb is the only independent variable. Thus, by using the regression model

$$\Delta\ \mathrm{HrQOL} = \alpha + \beta\Delta\mathrm{Hb} + \varepsilon$$

a less conservative determination can be made for both within-group and between-group MIDs for changes in HrQOL scores as based upon a 1-g/dL change in Hb. The within-group HrQOL MID is the HrQOL change as estimated from the regression parameters when letting the change in Hb equal 1 (i.e., the within-group HrQOL MID is simply $\alpha + \beta$). If one wanted to calculate the within-group HrQOL MID associated with a 2-g/dL change in Hb, then the MID is $\alpha + 2\beta$, and some analysts and clinicians might prefer this higher bar for the external standard.

The between-group HrQOL MID is slightly more difficult to visualise, but we suggest that the between-group HrQOL MID equals the slope of the regression line (i.e., the between-group HrQOL MID is β). What makes the slope of this regression intuitively difficult to understand is that the variables in the regression already represent change, thus the slope represents the change of the change of these variables. The slope of the regression can be interpreted as the expected difference in HrQOL change between groups that are separated by 1 g/dL change in Hb. Consider, for example, one hypothetical patient group that experienced a change in Hb of 1.8 g/dL and another hypothetical patient group that experienced a change in Hb of 2.8 g/dL (a difference of 1 g/dL change in Hb). Thus, the between-group difference in HrQOL change in this example is: $(\alpha + 2.8\beta) - (\alpha + 1.8\beta) = \beta$. From this, we see that the between-group difference in HrQOL change is equal to the slope of the regression line (i.e., β). Alternatively, if one wished to calculate the expected difference in HrQOL change between groups that were separated by 2 g/dL change in Hb, then the expected between-group change in HrQOL would be 2 times the slope of the regression line (i.e., 2β). An example of using a linear regression model to estimate within- and between-group MIDs, based on FACT-G Total data from Littlewood and colleagues (2001), is shown in Fig. 1. The SAS® procedure PROC REG was used to perform the linear regressions.

3. Results

Table 2 shows a comparison of (stable versus improved) MIDs and trial-reported differences in HrQOL change between treatment groups. For the FACT-G Total, the MID (i.e., the difference in HrQOL between patients with stable Hb (change of between −1.0 and 1 g/dL) and those with an Hb change $\geqslant$1.0 g/dL) was 2.54. In the clinical trial, the difference in the FACT-G Total between the epoetin alfa-treated group and the placebo group was 6.06. Since the HrQOL difference seen in the trial was larger (in this case, substantially larger) than the MID, we conclude that the change in HrQOL reported by the clinical trial was clinically significant. In fact, clinically significant differences were seen for all 5 cancer-specific HrQOL measures.

Minimally important differences for HrQOL scales are shown in Table 2 (all scales), and illustrated in Figs. 2–6 (cancer-specific, Hb-sensitive scales). Also shown in Table 2 and Figs. 2–6 are the actual differences in change scores between treatment arms in the clinical trial. As these results show, between-group differences for patients treated with epoetin alfa versus placebo exceeded the MIDs for every FACT and CLAS measure. Smaller MIDs and differences in change scores were seen for the general SF-36 PCS and SF-36 MCS.

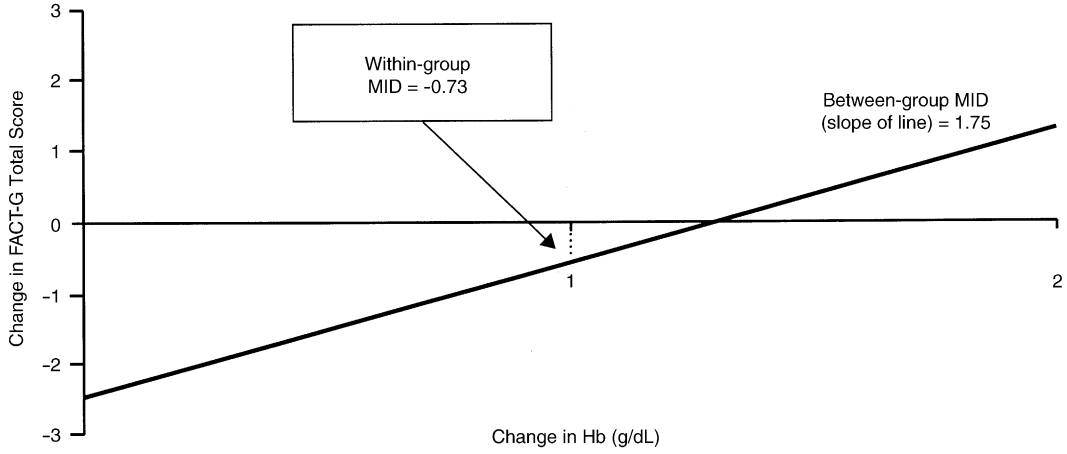

Fig. 1. An example of regression analysis based on the Functional Assessment of Cancer Therapy-General (FACT-G Total) data from a double-blind, placebo-controlled, randomised trial of the effects of epoetin alfa in anaemic cancer patients who received non-platinum chemotherapy for non-myeloid malignancies [19]. The within-group health-related quality of life (HrQOL) minimally important difference (MID) for change in score is the difference between the intercept and the slope of the regression line at the point of the 1-g/dL change in Hb. The between-group HrQOL MID for change in score equals the slope of the regression line.

Table 2
MIDs versus differences in change scores by treatment groups

HrQOL scales	By haemoglobin improvement			By treatment arm		
	Stable	Improved	MID	Epoetin alfa	Placebo	Difference
FACT-G Total	−0.15	2.39	2.54	2.49	−3.57	6.06
FACT-An Fatigue subscale	−0.69	3.55	4.24	2.97	−2.18	5.15
CLAS: energy level	−0.96	8.65	9.61	8.06	−5.81	13.87
CLAS: daily activities	−0.45	8.29	8.74	7.51	−5.99	13.50
CLAS: overall QOL	−3.37	6.44	9.81	4.79	−5.97	10.76
SF-36: PCS	−0.92	2.16	3.08	1.77	−0.53	2.30
SF-36: MCS	2.49	1.71	−0.78	2.14	−0.25	2.39

MID, minimally important difference; FACT-G Total, Functional Assessment of Cancer Therapy-General; FACT-An, Functional Assessment of Cancer Therapy-Anemia; CLAS, Cancer Linear Analog Scale (also known as Linear Analog Scale Assessment, or LASA); SF-36, Short-Form 36; PCS, Physical Component Summary; MCS, Mental Component Summary.

Table 3
Regression coefficients and mean QOL change scores

HrQOL scales	Slope estimate (S.E.)	Epoetin alfa	Placebo	Difference
FACT-G Total	1.75 (0.40)	2.49	−3.57	6.06
FACT-An Fatigue subscale	1.73 (0.35)	2.97	−2.18	5.15
CLAS				
Energy level	4.21 (0.74)	8.06	−5.81	13.87
Daily activities	5.08 (0.80)	7.51	−5.99	13.50
Overall QOL	4.66 (0.74)	4.79	−5.97	10.76
SF-36				
PCS	1.05 (0.24)	1.77	−0.53	2.30
MCS	0.70 (0.33)	2.14	−0.25	2.39

QOL, quality of life; FACT-G Total, Functional Assessment of Cancer Therapy-General; FACT-An, Functional Assessment of Cancer Therapy-Anemia; CLAS, Cancer Linear Analog Scale (also known as Linear Analog Scale Assessment or LASA); SF-36, Short-Form 36; PCS, Physical Component Summary; MCS, Mental Component Summary; S.E., standard error.

Table 3 shows the slope regression coefficients derived from regressing the change in Hb on the change in HrQOL. As noted above, we can interpret the slope of these regressions as being associated with a 1-g/dL difference in change in Hb. Table 3 indicates that, for every HrQOL endpoint, the between-group difference in mean HrQOL change observed in the Littlewood and colleagues 2001 study [19] is greater than the regression slope coefficient. This indicates that the observed between-group differences in changes in HrQOL are larger than a threshold value as anchored by a 1-g/dL difference in changes in Hb.

4. Discussion

HrQOL instruments often produce results or scores that physicians are not able to evaluate concerning their

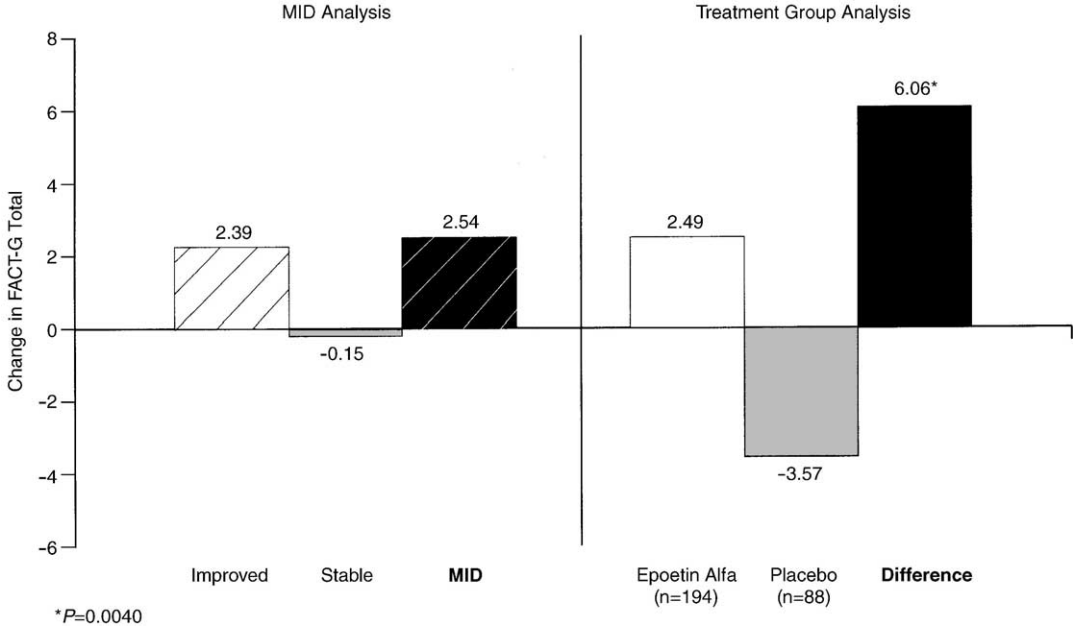

Fig. 2. Minimally important difference (MID) for change in Functional Assessment of Cancer Therapy-General (FACT-G Total) and analysis by treatment group. The difference in FACT-G Total scores between the epoetin alfa group and the placebo group was statistically significant ($P = 0.004$) and, as shown versus the MID, was also clinically significant.

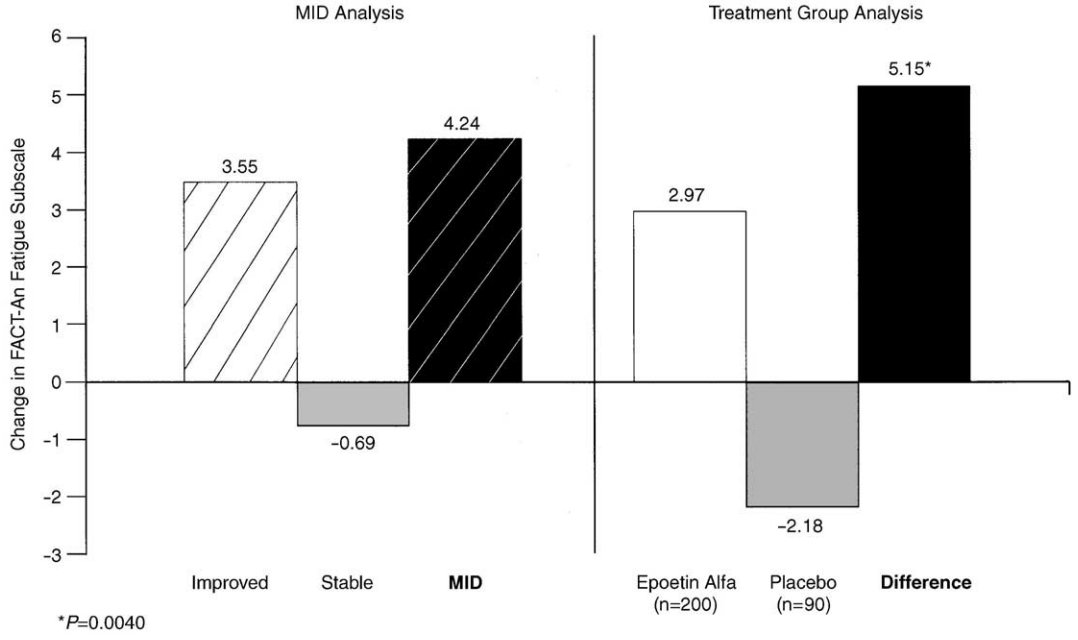

Fig. 3. Minimally important difference (MID) for change in Functional Assessment of Cancer Therapy-Anemia (FACT-An) (fatigue subscale) and analysis by treatment group. The difference in FACT-An fatigue subscale scores between the epoetin alfa group and the placebo group was statistically significant ($P = 0.004$) and, as shown versus the MID, was also clinically significant.

clinical importance, such as they would with a clinical marker like a 10% increase in blood pressure [1]. Alternative means are therefore needed for interpreting these valuable gauges of patient well-being and functioning. Analysis of MID is a means of translating changes in an HrQOL instrument score into terms that are clinically meaningful [1]. The MID has been described as the "smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate...a change in the patient's management" [1]. Thus, the MID has clinical significance.

In this study, which included the effects of anaemia on HrQOL, Hb level was considered the best external criterion upon which to base an analysis of MID. It satisfied the requirement for substantial correlation with HrQOL domains, as increases in Hb have been asso-

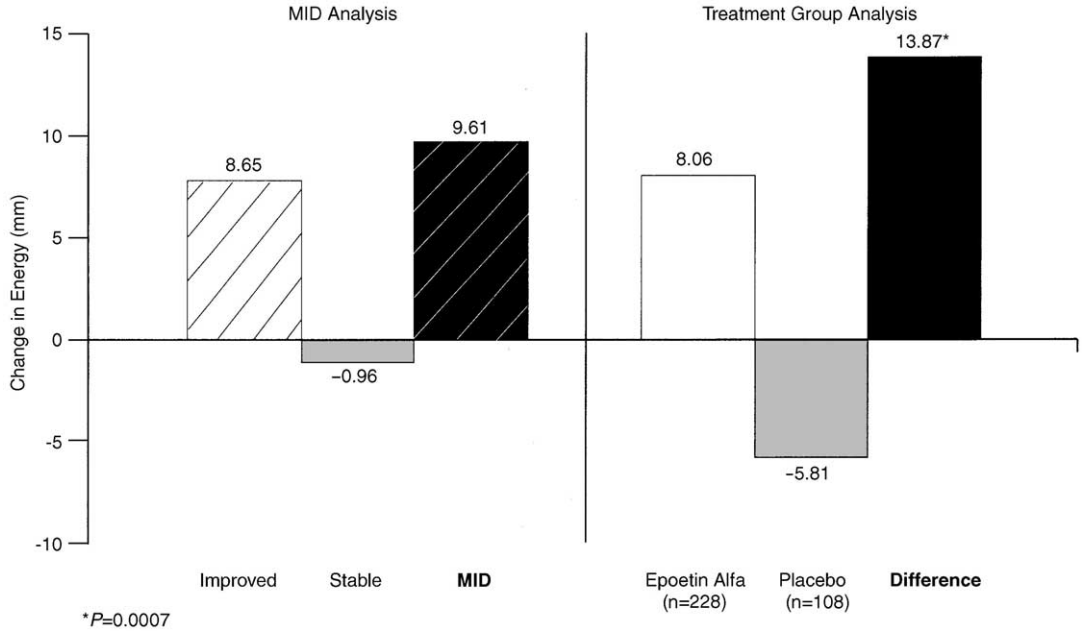

Fig. 4. Minimally important difference (MID) for change in the Cancer Linear Analog Scale (CLAS, also known as the Linear Analog Scale Assessment, or LASA) score for energy level and analysis by treatment group. The difference in CLAS scores between the epoetin alfa group and the placebo group was statistically significant ($P = 0.0007$) and, as shown versus the MID, was also clinically significant.

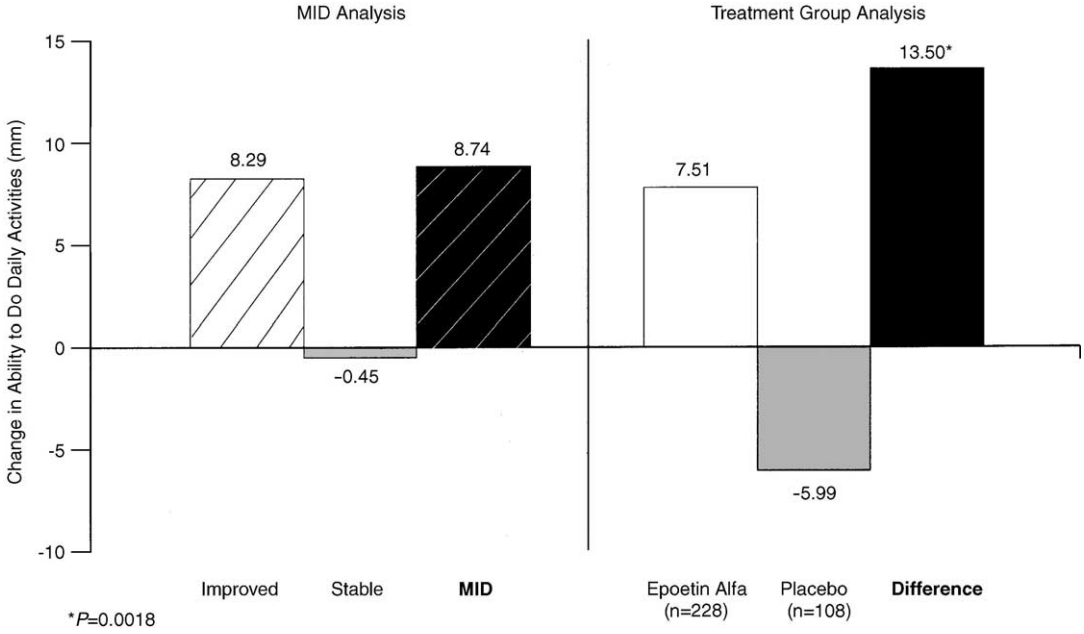

Fig. 5. Minimally important difference (MID) for change in the Cancer Linear Analog Scale (CLAS, also known as the Linear Analog Scale Assessment, or LASA) score for ability to do daily activities and analysis by treatment group. The difference in CLAS scores between the epoetin alfa group and the placebo group was statistically significant ($P = 0.0018$) and, as shown versus the MID, was also clinically significant.

ciated with increases in HrQOL in numerous large clinical studies [17–20]. In addition, Hb is the biomarker most often used to evaluate anaemia [24]. Further support for Hb level as the best external criterion for this analysis arises from the observation that Hb level is related to other important clinical and policy variables, such as the administration of blood transfusions [24–26]. Hb level is a relevant marker in medical standards of practice, and it is possible to identify the threshold by which even the smallest expected decrease in Hb would warrant medical intervention [24–26]. In Littlewood and colleagues' study [19], patients assigned to epoetin alfa

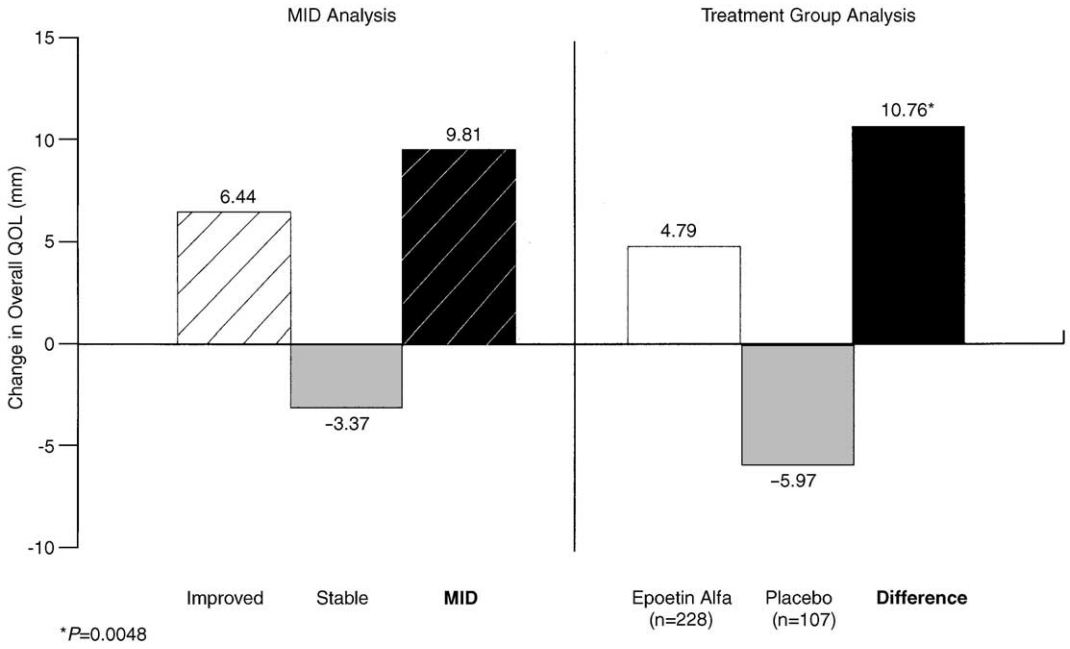

Fig. 6. Minimally important difference (MID) for change in the Cancer Linear Analog Scale (CLAS, also known as the Linear Analog Scale Assessment, or LASA) score for overall quality of life (QOL) and analysis by treatment group. The difference in CLAS scores between the epoetin alfa group and the placebo group was statistically significant ($P = 0.0048$) and, as shown versus the MID, was also clinically significant.

treatment achieved approximately a 1.5-g/dL greater increase in Hb levels than placebo-treated patients and received significantly fewer transfusions, suggesting that a 1-g/dL increase was large enough to affect medical practice with respect to transfusions [19]. Because physicians are willing to prescribe a transfusion based on the expectation of a resultant Hb increase, it may be concluded that an Hb change of 1 g/dL is a clinically meaningful marker.

In the initial analysis, all patients who achieved the minimum improvement in Hb of 1 g/dL were grouped together in the improved group, resulting in a conservative HrQOL MID estimate. It was reasoned that if the observed HrQOL change exceeds this conservative estimate of minimal importance, it also exceeds a more realistic estimate of the minimal clinically important change. To more closely focus upon the change in HrQOL associated with a 1-g/dL change in Hb, an additional method (linear regression analysis) for calculating MID was adopted that was not subject to these limitations. Results of the regression analysis demonstrated that the observed between-group differences in changes in HrQOL were substantially larger than a threshold value anchored by a 1-g/dL difference in change in Hb. These results suggest that the effect of epoetin alfa on HrQOL is, in fact, more robust than what was shown by the 'improved versus stable' MID calculations.

The HrQOL assessments selected for primary analysis included two anaemia- and cancer-specific instruments (FACT and CLAS), and a general instrument designed for use with many populations and in a number of settings (SF-36). Predictably, in this patient population, the five anaemia- and cancer-specific HrQOL scales emanating from FACT and CLAS all showed large, positive MIDs, while the SF-36 PCS and MCS did not (although they favoured epoetin alfa as point estimates). However, the SF-36 contributed an index of potential adverse consequences and unanticipated treatment effects, and served as a means for assuring that no decrement in HrQOL was associated with epoetin alfa treatment.

The HrQOL MID calculations presented in this report were confirmed by analysis of MID values calculated using a community-based, phase IV study [18]. The MID values calculated from the community-based study were directly compared with the between-group differences in HrQOL as observed in the Littlewood and colleagues study [19]. MID values were derived from the community-based study using both the difference in HrQOL between stable and improved groups method and the regression method outlined in this report. MID values as calculated by both methods were FACT G Total: 5.56, 1.77; FACT-An Fatigue subscale: 4.75, 1.63; CLAS Energy: 9.29, 3.54; CLAS Ability to Do Daily Activities: 8.06, 3.25; and CLAS Overall QOL: 9.68, 3.46, respectively (SF-36 data were not collected in the community-based study). The difference in mean change in Hb between the stable and the improved groups from the community-based study was approxi-

mately 2.9 g/dL, again representing an overestimation of the HrQOL MID. Therefore, MIDs as calculated in the improved versus stable analysis are greater than those derived by the more precise linear regression analysis. The results of these analyses confirm the findings from the MID analyses based on the Littlewood and colleagues data [19], that epoetin alfa-attributable improvements in HrQOL are clinically, as well as statistically, significant.

Although the linear regression analysis allows for a less conservative estimation of the between-group MID, this technique has limitations. One major limitation is that the relationship between change in Hb and change in HrQOL may not be linear. If so, a non-linear regression analysis can be conducted and the MIDs can be calculated in the manner indicated above, but in this case using the instantaneous slope of the curve to derive the between-group MID. If, however, the non-linear specification of the model makes no theoretical sense or if its non-linear terms are not significant at a sufficient alpha level, then there is no utility in calculating MIDs from the non-linear regression parameter estimates. We checked for non-linear associations between change in Hb and change in each of the HrQOL scales and rejected a non-linear relationship in every case. Thus, the linear regression parameter estimates were used to calculate the MIDs for this analysis.

The information provided by these MID analyses is important because it gives clinical relevance to changes in HrQOL as evaluated in clinical trials. It should be noted that a limitation of these analyses is that both of the methods used to calculate HrQOL MIDs rely upon the pooling of patient data across treatment groups. In so doing, an important assumption is being made. Namely, it is assumed that any change in HrQOL due to treatment intervention is mediated by change in Hb level. Thus, whether or not a particular patient has received active treatment as opposed to placebo, the main driver for change in HrQOL is assumed to be the change in Hb. To the extent that this assumption is not true for any particular HrQOL measure, these methods for calculating MIDs for that measure cannot be perfectly accurate. Many internal and external factors affect QOL, including non-biomedical determinants (e.g., if a patient experiences a change in personal situation such as a divorce or financial setback, a decrease in fatigue may not have a substantial effect on the patient's QOL). However, these effects occur in both the treatment and control groups and are assumed to be balanced. Therefore, an increase in Hb generally translates to an improvement in QOL, but in individual cases, this may not hold true.

The effects of cancer-related fatigue have been well documented, and it is now the most common symptom reported by cancer patients [16,27,28]. Its adverse effects involve multiple QOL dimensions—physical, emotional, functional, and social. A recent study of 379 cancer patients with a prior history of chemotherapy showed that 76% experienced fatigue at least several days each month, and 60% ranked it as the side-effect with the greatest impact on daily living [16]. These findings are underscored by the words of a British patient who underwent chemoradiotherapy for non-Hodgkin's lymphoma: "Everybody tells you that you are going to feel ill, everybody tells you that you are going to lose your hair, everybody says that you will put on weight, but nobody says you won't be able to move hardly, you won't be able to get up, you won't be able to do your normal daily things. Fatigue is a very understated...part of the treatment...It was very, very hard to come to terms with" (Paul Harrison, oncology patient). Another study further elucidated the impact of fatigue on the social domain, showing that patients experiencing fatigue reported adverse effects on intimacy with their partners and on relationships with family and friends [15]. Among patients who worked, 75% reported changing their employment status as a result of fatigue [16]. They also reported that their primary caregivers took additional time off from work (20%), accepted fewer responsibilities (18%), or worked reduced hours (11%). 12% of primary caregivers used unpaid family leave or were forced to cease working altogether. These data emphasise the broad impact of fatigue and illustrate how essential QOL analyses are to understanding the economic burden of disease and implementing cost-effective healthcare interventions.

Data show that the impact of fatigue is underappreciated by physicians. A telephone survey of 100 000 randomly selected households including 419 cancer patients and a separate mail survey of 197 unrelated randomly sampled oncologists found that despite the high prevalence and adverse impact of cancer-related fatigue, it was seldom discussed between patients and their oncologists and was infrequently treated [15]. Most oncologists (80%) believed fatigue is overlooked or undertreated, and 74% of patients considered fatigue a symptom to be endured and accepted. While oncologists believed that pain adversely affected their patients to a greater degree than fatigue (61% versus 37%), patients considered fatigue to have a greater adverse effect on their daily lives than pain (61% versus 19%). Only 50% of patients discussed treatment options for fatigue with their oncologists, and only 27% reported that their oncologists recommended any treatment for fatigue. When used, treatments for fatigue were generally perceived by patients to be successful.

A recently published meta-analysis of clinical trials evaluating the use of epoetin alfa in anaemia associated with cancer and chemotherapy concluded that although epoetin alfa was effective for reducing transfusion requirements across all haemoglobin categories, evidence was insufficient to determine whether initiating

epoetin alfa treatment earlier results in better HrQOL than waiting until Hb levels decline below 10 g/dL [29]. This article, which focused largely on transfusions, failed to take into account that patients treated at higher Hb levels appeared to experience the same magnitude of HrQOL benefit in response to Hb change as patients whose Hb levels had declined below 10 g/dL. This important benefit to patients has been reinforced by an incremental analysis of two clinical studies ($N = 4382$), which found that greatest incremental HrQOL improvement observed when Hb level increased from 11 to 12 g/dL (range 11–13 g/dL) [30].

Important areas of patient care that are receiving increasing attention are quality of end-of-life and quality of dying. Based on concepts elicited from literature review, interviews with patients with and without chronic and terminal disease, and consideration of desirable instrument properties, a recent article proposed a model for evaluating the quality of death and dying [31]. This is defined as the degree to which the patient's preferences for dying and the moment of death match with observations of the patient's actual experience as reported by others. Qualitative data analysis yielded six domains: symptoms and personal care, preparation for death, moment of death, family, treatment preferences, and whole-person concerns. Similar models proposed by Stewart and colleagues and Byock and colleagues focus on developing frameworks that emphasise QOL and evaluate care that patients receive at the end of life [32,33]. Definition of these models will assist in evaluating interventions to improve quality of end-of-life care.

5. Conclusions

The MID for changes in HrQOL in anaemic cancer patients can be accurately assessed by relating changes to a 1 g/dL change in Hb level. Results from the analyses reported here have underscored the positive effect of epoetin alfa observed in the clinical trial, namely, that significantly increased Hb levels result in significantly increased HrQOL scores that are also clinically meaningful. Furthermore, the analyses of MID provide a valid method to give clinical relevance to changes in HrQOL as evaluated in clinical trials. Our analyses provide a context for HrQOL measurements and a clear understanding to physicians of how to manage anaemia and fatigue in cancer patients undergoing chemotherapy.

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Appendix

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