The minimal important difference of the King’s Brief Interstitial Lung Disease Questionnaire (K-BILD) and forced vital capacity in interstitial lung disease

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KEYWORDS
Idiopathic pulmonary fibrosis;
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Interstitial lung disease

Summary
Health status and forced vital capacity (FVC) are widely used outcome measures of interstitial lung disease (ILD) but there is a paucity of studies reporting the minimal clinically meaningful change in these parameters. A study was undertaken to assess the minimal important difference (MID) of an ILD specific health status questionnaire, the King’s Brief ILD questionnaire (K-BILD) and that of FVC in a range of ILDs.

57 patients with ILD (17 idiopathic pulmonary fibrosis; IPF) completed the K-BILD (score range 0–100) at 2 separate clinic visits. Patients underwent spirometry at both visits. The MID was determined by a range of distribution methods (Standard error of mean: SEM and
Introduction
Forced vital capacity (FVC), the 6 minute walk test (6MWT) and health status are widely used outcome measures of interstitial lung disease (ILD). Desaturation during the 6MWT has been shown to be predictive of mortality in ILD [1]. Recent studies in idiopathic pulmonary fibrosis (IPF) have shown that small changes in FVC are associated with clinically significant changes in health status and mortality [2, 3]. It is not known if small changes in FVC are clinically important in a range of ILDs. Health status in ILD can be assessed with a number of recently developed disease specific questionnaires [4-6]. The minimal important difference (MID) for these tools has not been reported. The MID, defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's (health care) management," is essential to facilitate meaningful clinical interpretation of health status data [7]. The aim of this study was to investigate the MID of a recently developed ILD specific health status questionnaire, the King's Brief Interstitial Lung Disease questionnaire (K-BILD) and also that of FVC in patients with a range of ILDs [8]. A range of anchor and distribution based methods were used to estimate the MIDs.

Methods
Subjects
Consecutive patients with ILD were recruited prospectively from secondary care (King’s College Hospital) and tertiary care (Royal Brompton Hospital) specialist clinics from January to August 2011. Clinical characteristics, co-morbidities and medications were recorded using a structured questionnaire. The cause of ILD was determined by a multi-disciplinary meeting of clinicians, radiologists and pathologists, following review of clinical characteristics, high resolution computerised tomography (HRCT) scan, lung function, and lung biopsy where available. The classification of ILD was consistent with international guidelines [9,10]. All patients gave written informed consent and the study was approved by London-Surrey Borders research ethics committee (ref: 09/H0806/74).

Protocol
All patients completed the K-BILD at the first clinic visit and again at a second visit greater than 4 weeks after the first, before review with the physician each time. Forced vital capacity (FVC) was assessed according to American Thoracic Society standards at both visits [11]. Patients also completed Global Rating of Change Questionnaires (GRCQ) at the second visit. For patients undergoing a therapeutic trial between visits, the details of treatment were recorded.

K-BILD
The K-BILD is a self-completed health status questionnaire that comprises of 15 items and a seven point Likert response scale [8]. Its validation has been recently reported [8]. It has three domains: psychological, breathlessness and activities and chest symptoms. The K-BILD total score and total score at the second visit was classified as unchanged (scores –1/0/1), a small change (–3, –2, 2, 3), a moderate change (–5, –4, 4, 5) or large change (–7, –6, 6, 7) [12].

Global rating of change questions (GRCQ)
The GRCQ is a 15-point scale used to determine the MID [12]. Patients rate the change in their lung health status between clinic visits. The response scale ranges from −7 (a great deal worse) to +7 (a great deal better). All subjects were asked to complete four GRCQs, relating to K-BILD domains and overall health status. The score for each GRCQ was classified as unchanged (scores –1/0/1), a small change (–3, –2, 2, 3), a moderate change (–5, –4, 4, 5) or large change (–7, –6, 6, 7) [12].

Minimal important difference of K-BILD
The recommended approach to estimating the MID is to use multiple anchor-based methods with a mixture of patient reported and clinical indicators, and to examine various distribution-based estimates as supportive information [13]. The MID should be representative of all these measures [13]. The K-BILD MID was estimated by both anchor-based and distribution methods to determine a mean and range. For the FVC anchor, subjects were categorised as per Swigris et al., “unchanged” if the change in FVC (%) between visits was 0–7%, “minimal change” if 7–12%, and “more than minimal change” if greater than 12% [14].
The MID using the GRCQ anchor was defined as the change in K-BILD health status corresponding to a small change in GRCQ score [7,12,15]. Two distribution-based methods were used to estimate the MID; standard error of measurement (SEM) and 0.3× effect size [13,16–18]. SEM was calculated as standard deviation at baseline multiplied by the square root of one minus the reliability coefficient (Cronbach’s alpha coefficient). Effect size was calculated by determining the mean difference in K-BILD score/standard deviation of baseline score.

### Minimal important difference of FVC

The MID for FVC (%) was determined by the SEM, 0.3× effect size and the change in FVC corresponding to a small change in GRCQ anchor.

### Analysis

SPSS software, version 18 (SPSS, Chicago, IL) was used for statistical analysis. Mean and standard deviation (SD) was used to describe parametric data. The global rating of change questionnaire score was expressed as an absolute number, i.e. when the change was negative, the sign was reversed as was the sign of the corresponding change in K-BILD score between visits [7,12]. Correlations were assessed with Pearson's (r) or Spearman's (ρ) coefficient for non-parametric or categorical data. Paired t tests were used for group comparisons. P < 0.05 was considered significant. The relative change in absolute FVC was reported as a percentage of the absolute baseline FVC.

### Results

57 patients with ILD were recruited for this study (17 patients Idiopathic Pulmonary Fibrosis, 18 connective tissue disease ILD (CTD-ILD), 9 idiopathic non-specific interstitial pneumonia (NSIP), 8 hypersensitivity pneumonitis, 4 idiopathic organising pneumonia, 1 lymphoid interstitial pneumonia (LIP)). Demographics and baseline characteristics are shown in Table 1. 50% of all patients (60% of IPF) had a TLCO <40% of predicted. 16 patients underwent therapeutic trials between clinic visits (4 methylprednisolone, 5 myco-phenolate mofetil, 2 cyclophosphamide, 1 rituximab, 1 hydroxyurea, 2 N-acetylcysteine, 1 pulmonary rehabilitation). The remaining patients did not undergo a change of therapy. The mean duration between visits was 9 months.

22(38%) patients deteriorated, 14(25%) improved and 21(37%) were unchanged between visits as rated by patients on the GRCQ scale. 21 patients reported no change in their health status, 13 small change, 19 moderate change and 4 large change (GRCQ categories). The moderate and large change GRCQ categories were combined for further analysis since the large change group contained a small numbers of patients (n = 4). Health status was reduced in all domains at baseline (Table 1). The K-BILD was a responsive instrument in those patients indicating a change in their health. There was a significant change in K-BILD total score from visit 1–2 in patients reporting a change in GRCQ: mean (SD) 62(21) vs. 50(19); mean difference 12; 95% confidence interval of difference 6 to 18; p < 0.01. The anchors used in this study were significantly related to changes in health status. There was a significant correlation between GRCQ and change in K-BILD (ρ = 0.52, p < 0.01; Fig. 3 Online Supplement) and between change in FVC and change in K-BILD (r = 0.41, p < 0.01; Fig. 4 Online Supplement). The change in health status scores for each GRCQ category is shown in Table 2. There were no significant differences in change in FVC or K-BILD scores between never smokers and current/ex-smokers (p = 0.40–0.96). The K-BILD total score MID corresponding to the FVC anchor was 10, GRCQ anchor: 8, 1× SEM: 6 and 0.3 ES: 7 (Table 2 and Fig. 1). The mean (range) MID for K-BILD total score was 8(6–10). The change in K-BILD total score for patients in the GRCQ MID category was; mean (SD) before 61(22) vs. after 53(15); mean difference 8; 95% confidence interval of difference 0 to 17; p = 0.059. The change in K-BILD score for each FVC category is shown in Fig. 2.

The mean (SD) change in FVC (visits 1–2) for each GRCQ category was: no change 2.6(8.1), small change (MID) 4.4(14.4) and moderate-large change 15.1(22.0). The MDs for FVC using GRCQ anchor method was 4%, 1× SEM method: 7% and 0.3 ES method: 7%. The mean (range) MID for FVC from all methods was 6(4–7). The mean (SD) FVC when calculated as an absolute change in % of predicted values for patients reporting no change and minimal change from visits 1–2 was 0.5(6.5)% and 2.2(10.3)% respectively.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics.</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>62(11)</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Ethnicity %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>South Asiana</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Smoking status %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Time since diagnosis (years)</td>
<td>4.0(4.4)</td>
<td></td>
</tr>
<tr>
<td>FVC % predicted (SD)</td>
<td>80(25)</td>
<td></td>
</tr>
<tr>
<td>TLCO % predicted (SD)</td>
<td>46(18)</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant medications at baseline (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Prednisolone + other</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>K-BILD psychological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>65(25)</td>
<td></td>
</tr>
<tr>
<td>Breathlessness and activities</td>
<td>46(28)</td>
<td></td>
</tr>
<tr>
<td>Chest symptoms</td>
<td>71(26)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>62(23)</td>
<td></td>
</tr>
</tbody>
</table>

All data are mean (standard deviation) unless otherwise stated. Definitions of abbreviations: FVC = forced vital capacity; TLCO = transfer factor of the lung for carbon monoxide as % predicted; K-BILD = King’s Brief Interstitial Lung Disease Questionnaire.

a South Asian patients originating from the India, Pakistan or Bangladesh.
Discussion

This is the first study to report the MID of FVC and ILD specific health status in a wide range of ILDs. The MID for FVC was a small change, 6% of baseline. The MID for K-BILD total score determined by a range of anchor and distribution methods was 6–10 units, average 8 units. Our study suggests that both FVC and health status questionnaires are responsive outcome measures and that they can be used to assess patients with ILD in the clinic.

We investigated the MID for K-BILD domain and total scores with a range of anchor and distribution methods. The MID range for total score was 6–10 units. The pre-specified method of determining the MID was an average of all methods, 8 units. We chose this in preference to any single method since it encompassed both the patients’ perspective and objective assessments. No single method of determining the MID has consensus opinion, however there is consensus that multiple methods and anchors should be used [13]. The GRCQ anchor method has been used by some investigators to determine the MID [12,19]. The GRCQ MID was within close approximation to that determined by other methods.

The GRCQ was significantly associated with change in K-BILD scores. The change in health status of patients reporting minimal change (GRCQ) approached statistical significance. A significant limitation of patient reported anchors such as GRCQ or SF36 (Du Bois et al.) is recall bias [3]. They are more likely to reflect current health status than change from a previous clinic visit [20]. The average time between assessments in our study was long, 9 months, similar to the study by Du Bois et al. (11 months) making recall bias a possibility [3]. However, FVC-anchor and distribution methods for determining the MID were not subject to recall bias. Further studies should utilise prospective patient rated scales that assess change, such as the Punum ladder, to eliminate recall bias [20]. It is possible that the FVC anchor method (7–12% change) overestimated the MID for K-BILD total score (10) since this change in FVC is larger than the MID for FVC determined in our study. We chose a 7–12% change in FVC as minimally important to be consistent with previous studies reporting the MID [14,21].

Swigris et al. investigated the MID of health status in IPF, assessed with St Georges Respiratory Questionnaire (SGRQ; Table 1). The minimal important difference of K-BILD.

<table>
<thead>
<tr>
<th>GRCQ change</th>
<th>FVC change</th>
<th>1 SEM</th>
<th>ES 0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same</td>
<td>Minimal important difference</td>
<td>FVC 0–7%</td>
<td>FVC 7–12%</td>
</tr>
<tr>
<td>K-BILD psychological</td>
<td>6.6(9.0)</td>
<td>1.5</td>
<td>7.6</td>
</tr>
<tr>
<td>K-BILD breathlessness and activities</td>
<td>5.2(7.6)</td>
<td>2.5</td>
<td>10.1</td>
</tr>
<tr>
<td>K-BILD chest</td>
<td>7.2(19.9)</td>
<td>2.0</td>
<td>13.7</td>
</tr>
<tr>
<td>K-BILD total</td>
<td>0.80(11.9)</td>
<td>1.3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

All data are mean (standard deviation). Positive and negative changes in each GRCQ and FVC category are grouped together. Definitions of abbreviations: GRCQ = global rating of change questionnaire; VC = vital capacity; SEM = standard error of baseline measurement; ES = effect size; K-BILD = King’s Brief Interstitial Lung Disease Questionnaire.

Figure 1 Change in K-BILD health status scores per global rating of change category. All data are mean (standard error mean: SEM). Definitions of abbreviations: K-BILD = King’s Brief Interstitial Lung Disease Questionnaire.

Figure 2 The relationship between longitudinal changes in forced vital capacity and health status. All data are mean (standard error mean: SEM). Definitions of abbreviations: K-BILD = King’s Brief Interstitial Lung Disease Questionnaire.
original differences between their study and ours. The SF36 and SGRQ are generic health and respiratory questionnaires respectively and the anchor used was a breathlessness scale (Transition Dyspnea Scale). The TDI focuses on a single symptom; it is not known if this impacts its ability to capture the wider change in a patients’ lung health. There are two other ILD specific health status questionnaires, a tool to assess quality of life-IPF (ATAQ-IPF) and SGRQ-IPF; their MID has not been reported [4,5].

There is a paucity of studies that have investigated the MID of FVC despite this being a widely used outcome measure of ILD. The MID of FVC has largely been evaluated against mortality in the past and a change of 10% is often considered significant [10,22,23]. Death cannot be characterised as minimally important and therefore estimates based on this approach may not appropriately reflect the smallest difference that is clinically important to patients [3]. A MID for FVC determined by the progression of disease based on symptoms is an alternative approach. We are aware of only one other study that has investigated the MID of FVC using a patient reported anchor of change [3]. Du Bois et al. investigated the MID of predicted FVC (%) in 363 patients with IPF over a 48 week interval. An item from the SF36 questionnaire that assesses change in general health over the previous year was used as the anchor. The MID using this patient rated anchor method was a change in FVC % predicted of 2.3%, similar to our finding (2.2% percent predicted or 4.4% relative change in absolute FVC; GRCQ method). The strength of the Du Bois study was its large size and fixed timings of assessments in a clinical trial setting. However, there were limitations with this study. The patient rated anchor was not lung specific; changes in non-pulmonary health during the study period may have influenced the patients’ response to the anchor question. The Du Bois study excluded patients with severe ILD, a clinically important subgroup and therefore their findings cannot be generalised to this population. Lastly, the FVC MID determined by the patient anchor approach was less than the change observed in patients reporting no change in health (2.3% vs. 2.8%). The reasons for this are unclear. Our study has addressed some of these limitations. We confirmed previous findings that a small change in FVC is perceived to be important by patients. Our study also suggests the K-BILD is a responsive health status outcome measure in ILD and the MID is a score of 8 units. The K-BILD may be useful in the assessment of the efficacy of therapy. This study should facilitate the clinical interpretation of health status and FVC outcome measures in ILD.

Conflict of interest statement

None declared.

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Appendix A

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.06.009.

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