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Minimal important difference in childhood interstitial lung diseases

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ABSTRACT

Background Monitoring disease progression in childhood interstitial lung diseases (chILD) is essential. No information for the minimal important difference (MID), which is defined as the smallest change in a parameter that is perceived as important prompting a clinician to change the treatment, is available. We calculated MIDs for vital signs (respiratory rate, peripheral oxygen saturation in room air, Fan severity score) and health-related quality of life (HrQoL) scores.

Methods This study used data from the Kids Lung Register, which is a web-based management platform that collects data of rare paediatric lung disorders with a focus on chILD. Data of vital signs and HrQoL scores (Health Status Questionnaire, chILD-specific questionnaire and PedsQL V.4.0) were collected. MIDs were calculated according to distribution-based (one-third SD) and anchor-based methods (using forced expiratory volume in 1 s and forced vital capacity) as anchors.

Results Baseline data of 774 children were used to calculate the following MIDs: respiratory rate 1.3 (z-score), O_2 saturation in room air 3.0%, Fan severity score 0.2–0.4, Health Status Questionnaire 0.4–0.8, chILD-specific questionnaire 4.4%–8.2%, physical health summary score 7.8%–8.9%, psychosocial health summary score 3.4%–6.9% and total score 5.1%–7.4%. Results of the responsiveness analysis generally agreed with the MIDs calculated.

Conclusions For the first time, we provide estimates of MIDs for vital signs and HrQoL scores in a large cohort of chILD using different methods.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The minimal important difference (MID) is the smallest change in a clinically relevant parameter, which would indicate a change in treatment. In the design of randomised clinical trials, MIDs assist in determining the selection of endpoints and calculating the sample size. The concept of MID directly addresses the limitation that studies may find statistical relationships that only have little or no clinical significance for patients. So far, MIDs for essential clinical parameters are not yet established for childhood interstitial lung diseases (chILD).

WHAT THIS STUDY ADDS

⇒ This study introduced MIDs in respiratory rate, peripheral oxygen saturation in room air, Fan severity score and health-related quality of life (HrQoL) scores in patients with chILD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The MID computed in this study will help judge the clinical relevance of changes in vital sings and HrQoL scores, design future clinical trials and support cost-effectiveness analyses of potential therapies.

INTRODUCTION

Childhood interstitial lung diseases (chILD) are a heterogeneous group of diffuse and mostly chronic respiratory disorders that mainly affect the lung parenchyma leading to impaired alveolar gas exchange.[1] This disease group is more diverse than interstitial lung diseases in adults, comprising at least 200 different conditions. In contrast to the broad diversity of underlying causes, the clinical presentation of chILD is non-specific and includes tachypnoea, crackles, hypoxaemia and failure to thrive.[1] The frequency of chILD is considered to be more than ten times smaller than in adults ILDs.[1] Reported were prevalences between 0.36/100 000 and 4.65/100 000 children[2 3] and incidences between 0.13/100 000 and 10.76/100 000 children.[2 4 5] As chILD-related mortality is high with estimates around 15%,[4 6] evaluating disease progression is particularly important.

When monitoring the clinical course of patients, the smallest change in a parameter that is considered important and prompting a potential change in treatment is defined as the minimal important difference (MID).[7–10] The MID provides a guide as to whether a change provides a minimum level of perceived benefit. The term was first described in 1989[8] and is now a well-established concept considered as a reliable method for calculating reference points for clinicians to consider altering a treatment and help interpreting the relevance of changes in parameters over time.[11–13] Also, in the design of randomised clinical trials (RCTs) MIDs assist in determining the selection of endpoints and calculate the sample size.[14 15] Finally, the concept of MID directly addresses the limitation that studies may find statistical relationships that only have little or

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Table 1 Baseline characteristics of the study cohort

Study cohort	
Total sample size	757 (100%)
Age (years)	7.3 (6.04; 0.1–18.0)
Sex	
Male	406 (53.6%)
Female	351 (46.4%)
Country the patient is treated in	
Germany	414 (54.7%)
UK	98 (12.9%)
Turkey	69 (9.1%)
Poland	39 (5.2%)
Italy	24 (3.2%)
Switzerland	21 (2.8%)
Spain	16 (2.1%)
Denmark	15 (2.0%)
Other*	61 (8.1%)
Disease category	
A1—DPLD-Diffuse developmental disorders	27 (3.6%)
A2—DPLD-Growth abnormalities deficient alveolarisation	52 (6.9%)
A3—DPLD-Infant conditions of undefined aetiology	139 (18.2%)
A4—DPLD related to alveolar surfactant region	185 (24.4%)
Ax—DPLD-unclear RDS in the mature neonate	14 (1.8%)
Ay—DPLD-unclear RDS in the almost mature neonate	14 (1.8%)
B1—DPLD related to systemic disease processes	81 (10.7%)
B2—DPLD-in the presumed immune intact host related to exposures	103 (13.6%)
B3—DPLD-in the immunocompromised host or transplanted	43 (5.7%)
B4—DPLD related to lung vessels structural processes	62 (8.2%)
B5—DPLD related to reactive lymphoid lesions	7 (0.9%)
Bx—DPLD-unclear RDS in the non-neonate	23 (3.0%)
By—DPLD-unclear non-neonate	8 (1.1%)

Data are presented as numbers (percent) or mean (range; SD).
*Belgium 13 (1.7%), Greece 10 (1.3%), Austria 8 (1.1%), Hungary 7 (0.9%), Portugal 5 (0.7%), Czech Republic 4 (0.5%), Netherlands 3 (0.4%), South Africa 3 (0.4%), Brazil 2 (0.3%), State of Palestine 1 (0.1%), Croatia 1 (0.1%), France 1 (0.1%), Luxembourg 1 (0.1%), Romania 1 (0.1%), Serbia 1 (0.1%).

no clinical significance for patients.[16] So far, MIDs for essential clinical parameters are not yet available for chILD.

There is no consensus yet as to how to calculate MIDs and several different methods defining MIDs have been introduced. It is recommended to include multiple approaches.[17 18] The most widely used methods include distribution-based and anchor-based approaches.[19] More commonly used is the distribution-based method.[7 12] This approach is determining MIDs based on the statistical characteristics of a variable, e.g. one-third of the SD have been selected as MID.[20] A major advantage of this approach is the simplicity of use, as it does not require external criteria. However, a disadvantage is the dependence on the reference sample making the calculation less generalisable.[21] The anchor-based approach to determine MIDs is generally considered superior and statistically more complex compared with the distribution-based method.[22 23] This method relates the change of a clinical or patient-reported outcome (PRO) score to an independent parameter, the anchor.[24] This second criterion can be an expert opinion, a clinically relevant test result or a score directly capturing the patient's preferences. The latter is considered optimal when calculating MIDs for health-related quality of life (HrQoL).[25] A detailed review characterising different methods used to calculate anchor-based MIDs in children has recently been published.[26]

The scope of this study was to establish MIDs for clinical variables commonly used in chILD in order to provide tools to assess the clinical relevance of disease progression and design RCTs.

METHODS

Kids Lung Register and study design

This study used data obtained from the Kids Lung Register (www.childeu.net). It is an observational, web-based management platform that prospectively collects clinical data of children diagnosed with chILD. Local physicians can participate as referring centre after all necessary contractual legal and ethical requirements have been fulfilled. Each patient and/or caregiver has to

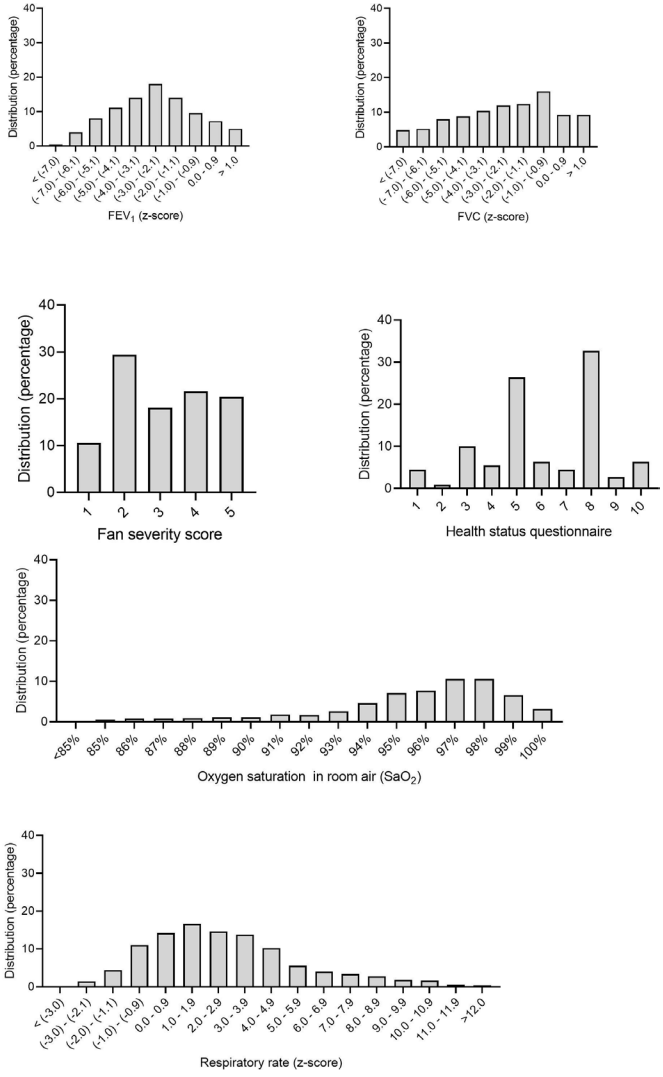

Figure 1 Distribution of FEV_1, FVC, Fan severity score, Health Status Questionnaire scores, oxygen saturation ratio in room air and respiratory rate (z-score) at baseline visit across patients with chILD. chILD, childhood interstitial lung diseases; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

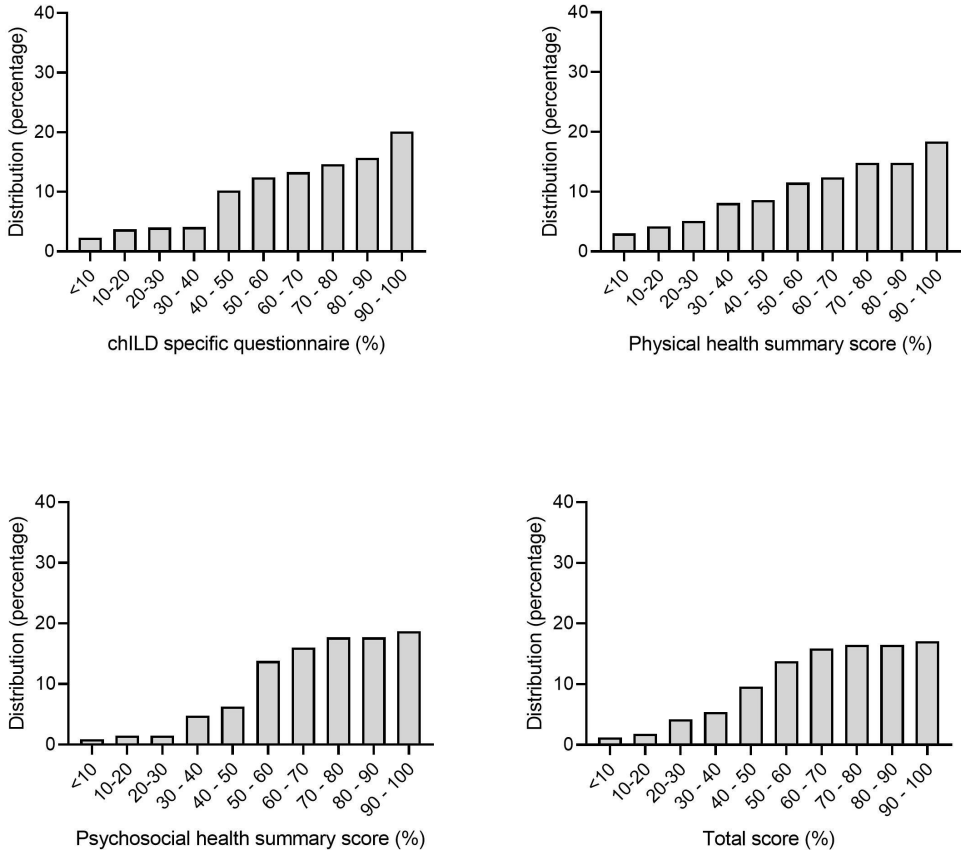

Figure 2 Distribution of chILD-specific questionnaire, Physical Health Summary score, Psychosocial Health Summary score and total score at baseline visit across patients with chILD. chILD, childhood interstitial lung diseases.

give age-appropriate assent and written informed consent. Clinical teams providing care are trained and provided with specific standard operating procedures (SOPs) as to how variables are collected and entered into the case report forms of the register. Following inclusion (baseline visit) completeness of data is checked and in a common meeting the diagnosis made by multidisciplinary teams in accordance with the clinical guidelines of the American Thoracic Society[27] and the European management platform for interstitial lung diseases in children.[28] Following this expert review process, data about the clinical course of the included patients are prospectively collected at defined study visits and entered by participating centres. During the first year, visits are scheduled every 6 months, then annually. The implementation and use of the Kids Lung Register have been described in detail elsewhere.[28]

Table 2 Correlation between vital signs as well as HrQoL and possible anchors: FEV_1 (z-score) and FVC (z-score)

Variable	FEV_1 (z-score) spearman's correlation coefficient (p value)	FVC (z-score) spearman's correlation coefficient (p value)
Vital signs		
Respiratory rate (z-score)	-0.194 (0.011)	-0.221 (0.004)
O2 saturation on room air	0.108 (0.004)	0.136 (0.051)
Fan severity score	-0.351 (<0.001)	-0.375 (<0.001)
HrQoL		
Health Status Questionnaire	0.335 (0.017)	0.302 (0.068)
chILD-specific questionnaire	0.339 (<0.001)	0.300 (<0.001)
Physical Health Summary score	0.393 (<0.001)	0.399 (<0.001)
Psychosocial Health Summary score	0.300 (<0.001)	0.303 (<0.001)
Total score	0.359 (<0.001)	0.344 (<0.001)

chILD, childhood interstitial lung diseases; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HrQoL, health-related quality of life.

Vital signs and Fan severity score

Vital signs included the respiratory rate, peripheral oxygen saturation (SpO_2) in room air and Fan severity score. The respiratory rate and oxygen saturation in room air were measured twice over 1 min in an awake patient after 5 min at rest. The measurements had to be at least 1 min apart. The stable average values were recorded. If the patient needed supplemental oxygen, the oxygen supplementation was withdrawn after 5 min at rest and the O_2-saturation was measured twice in the course of 1 min. If the SpO_2 fell below 80% oxygen is placed back and no value noted. Respiratory rate z-scores were derived from.[29] The severity of illness was analysed using the adapted disease Fan severity score and categorised as follows: (1) asymptomatic, (2) symptomatic with normal room air oxygen saturation under all conditions, (3) symptomatic with normal resting room air saturation, but abnormal saturation (SaO_2<90%) with sleep or exercise, (4) symptomatic with abnormal resting room air saturation <90% and (5) symptomatic with pulmonary hypertension.[30 31]

Pulmonary function testing

All children older than 5 years were asked to perform lung function testing. Absolute litres of forced expiratory volume in 1 s

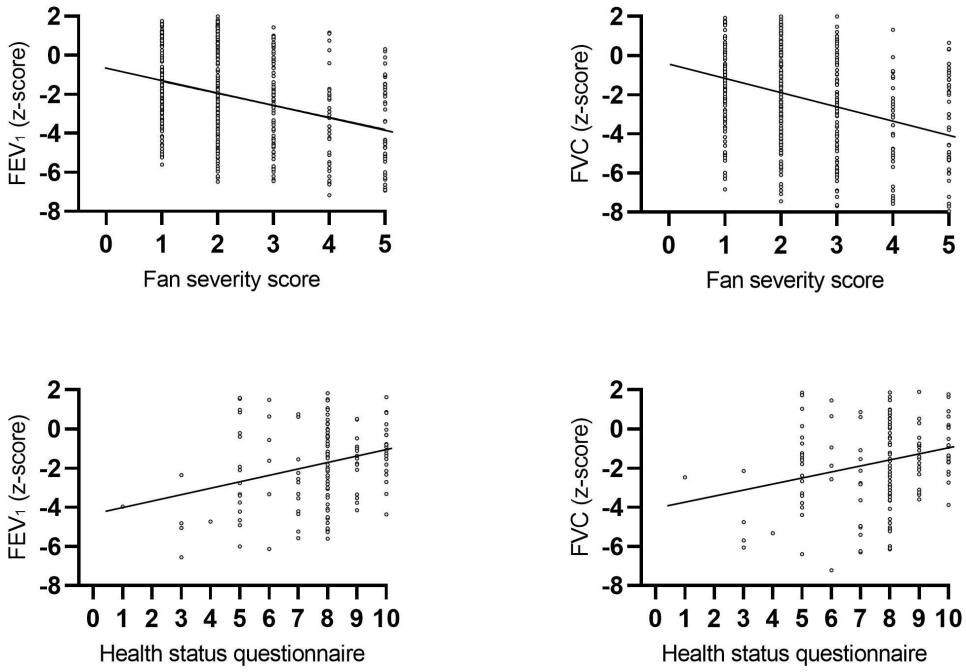

Figure 3 Association between Fan Severity Score and Health Status Questionnaire scores assessed from patients with FEV_1 (z-score) and FVC (z-score) as anchors. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

(FEV_1) and forced vital capacity (FVC) were recorded. Age-specific and sex-specific scores (z-scores) were calculated using the Global Lung Function Initiative reference values.[32]

Health-related quality of life

At every study visit, the caregivers were asked to estimate the children's medical condition on a scale from 0 (very bad) to 10 (perfect): the Health Status Questionnaire. Thereafter, caregivers were handed PROs. The questionnaires were filled by the caregivers (proxy-reported) including the chILD-specific questionnaire and PedsQL 4.0. The PedsQL 4.0 consists of three different subscales: physical health summary score, psychosocial health summary score and total score. All questionnaires were available in different languages and age versions. Feasibility, reliability and validity as well as internal consistency for chILD-specific questionnaire and PedsQL V.4.0 have been proven.[33]

Statistics

The statistical evaluation of the data was done with SPSS software for statistical analyses (V.26.0) and GraphPad Prism (V.8.4.3). Demographic data are reported as means (range, SD) or numbers (per cent).

Calculation of MIDs and responsiveness analysis

As a combination of anchor-based and distribution-based methods is recommended to determine MIDs,[17 20] both methods were used in this study assessing baseline visit scores. For the distribution-based method, the SD of the assessed scores was determined. The MIDs are defined by one third of the calculated values. This method has been suggested by Yost and Eton.[19]

The recommended statistical analysis to determine MIDs using the anchor-based method is more complex.[7] We choose the same approach that has been recently published in a study defining MIDs in adults with a broad spectrum of ILDs.[34] First, we identified the pulmonary function as relevant to patients and lung function testing results (FEV_1 and FVC) as potential anchors. The relationship between the anchors and variables (respiratory rate, oxygen saturation on room air, Fan severity and HrQoL scores) was assessed using Spearman's correlation. As recommended, the anchors were only included in the final analysis if the calculation proved at least a moderate correlation between the anchors and the outcome variable (r value $r \geq |0.3|$).[17 19] If an acceptable relationship was revealed, we performed an unadjusted linear regression between the anchors (independent variable) and the outcome variable (dependent variable). Finally, the MIDs were generated from the corresponding regression equations based on a z-score of 1.64 for FEV_1 and FVC, as this number was established for the lower limit of normal for spirometry.[35 36]

To evaluate for possible changes of vital sings and HrQoL scores, a responsiveness analysis was performed at the follow-up visit. An absolute FEV_1 and FVC z-score change of 1.64 between baseline and the follow-up visit was considered significant, as this number is representing the lower, respectively upper 5% limit of normal. Children were categorised into three groups: group 1 (deteriorated) ΔFEV_1 or $\Delta FVC < -1.64$ (z-score), group 2 (same) -1.64 (z-score) $< \Delta FEV_1$ or $\Delta FVC < 1.64$ (z-score) and group 3 (improved) ΔFEV_1 or $\Delta FVC > 1.64$. The corresponding changes (means) for vital signs, Fan severity and PRO scores, were calculated. If the 6 months follow-up visit was missed, results were calculated using the 1-year follow-up.

RESULTS

Study population

A total of 757 children were included at baseline (table 1). Mean age was 7.3 years (SD 6.04; 0.1–18.0). Males (53.6%) and females (46.4%) were almost equally distributed. Most patients were treated in Germany (54.7%), UK (12.9%), Turkey (9.1%), Poland (5.2%), Italy (3.2%), Switzerland (2.8%), Spain (2.1%) and Denmark (2.0%). The spectrum of chILD categories and subcategories observed was broad. Characteristics of the study population are listed in table 1.

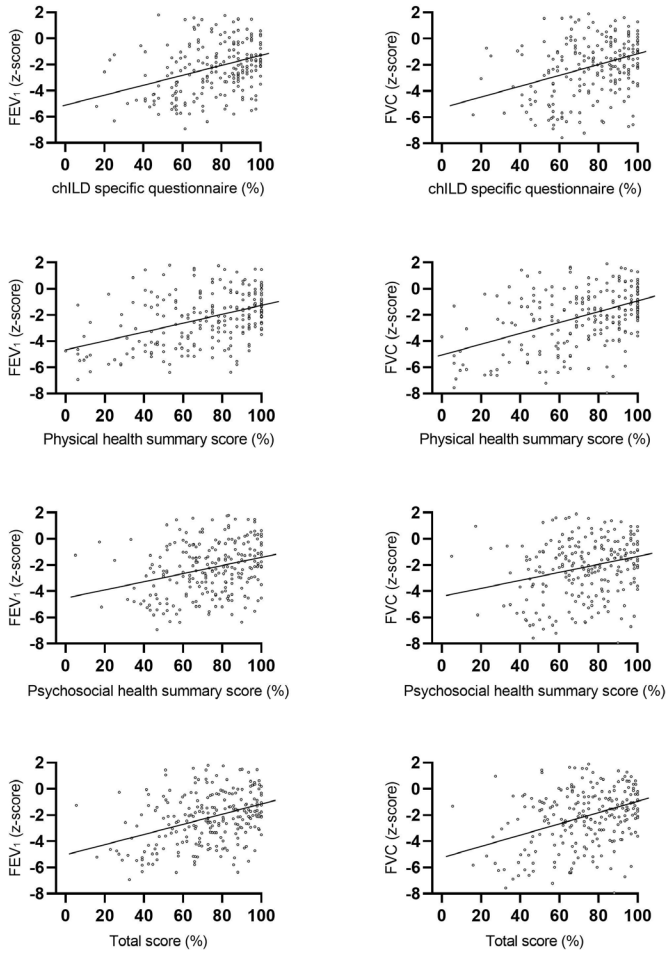

Figure 4 Association of chILD-specific questionnaire and Physical Health Summary score, Psychosocial Health Summary score and total score assessed from patients with FEV_1 (z-score) and FVC (z-score) as anchors. chILD, childhood interstitial lung diseases; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Vital signs and HrQoL

At baseline, respiratory rate of 535, oxygen saturation in room air of 490, Fan severity score of 742 and spirometry results of 242 children were available to calculate MIDs. There were no differences between children usually able to perform spirometry on an acceptable level (older than 5 years) with and without recorded PFT data regarding disease category (p=0.053) or being symptomatic (p=0.285). 364 HrQoL questionnaires were completed. The distribution of spirometry results was almost normal, Fan severity score, Health Status Questionnaire scores and oxygen saturation were skewed to the left. Respiratory rate (z-score) was tailed to the right (figure 1), whereas the chILD-specific questionnaire and PedsQL V.4.0 scores had a ceiling effect (figure 2).

The correlation analysis between spirometry results and respiratory rate as well as oxygen saturation in room air revealed only a small association, whereas between spirometry results and Fan severity, Health Status Questionnaire, chILD-specific questionnaire and all PedsQL V.4.0 scores a moderate or better correlation was found (table 2, figures 3 and 4).

Estimates and responsiveness of MID

Estimates of the MIDs for respiratory rate (z-score), oxygen saturation in room air (per cent), Fan severity, Health Status Questionnaire, chILD-specific questionnaire and PedsQL V.4.0 scores are provided in table 3. Calculations of the distribution based MIDs were performed for all variables. For respiratory rate (r=0.194 for FEV_1; r=0.221 for FVC) and oxygen saturation in room air (r=0.108 for FEV_1; r=0.136 for FVC) no anchor-based MIDs were calculated; analyses revealed distribution-based MIDs of 1.3 and 3.0%, respectively. Distribution-based MIDs for Fan severity, Health Status Questionnaire, chILD-specific questionnaire and all PedsQL V.4.0 scores provided higher scores than anchor-based MIDs. The distribution-based MIDs calculated for Fan severity and Health Status Questionnaire score were 0.4 and 0.8, whereas the anchor-based scores ranged from 0.2 to 0.4 and 0.4 to 0.5, respectively. The distribution-based MIDs for chILD-specific questionnaire and PedsQL V.4.0 scores ranged from 6.9 to 8.9, whereas the anchor-based MIDs ranged from 3.4 to 8.3, depending on which anchor was used.

Results of the responsiveness analysis generally agreed with the MIDs previously calculated (table 4). A change of the z-score in FEV_1 or FVC above |1.64| between two study visits resulted in change of vital signs or HrQoL scores above the corresponding MIDs. In contrast to that, smaller z-score changes of the spirometry results revealed no meaningful changes of vital signs or HrQoL scores.

Table 3 MID calculation (and 95% CIs) for vital signs and HrQoL

Variable	Distribution based MID (1/3 SD)	Anchor based MID (FEV_1)	Anchor based MID (FVC)
Vital signs			
Respiratory rate (z-score)	1.3	-*	-*
O2 saturation on room air (percent)	3.0	-*	-*
Fan severity score	0.4	0.2 (0.2 to 0.3)	0.3 (0.2 to 0.3)
HrQoL			
Health Status Questionnaire	0.8	0.5 (0.3 to 0.6)	0.4 (0.2 to 0.5)
chILD-specific questionnaire (percent)	8.2	5.2 (3.2 to 7.0)	4.4 (2.7 to 6.0)
Physical Health Summary score (per cent)	8.9	8.3 (6.1 to 9.2)	7.8 (6.0 to 9.9)
Psychosocial Health Summary score (percent)	6.9	4.4 (2.6–6.3)	3.4 (2.0 to 5.1)
Total score (per cent)	7.4	5.8 (4.1 to 7.8)	5.1 (3.4 to 6.8)

*No anchor-based MIDs were calculated as Spearman's correlation coefficient did not indicate at least a moderate correlation (r value ≥ |0.3|) between the variables and anchors.
chILD, childhood interstitial lung diseases; FEV1, forced expiratory volume in 1; FVC, forced vital capacity; HrQoL, health-related quality of life; MID, minimal important difference.

DISCUSSION

This is the first study of children diagnosed with chILD to provide estimates of MIDs for this population. No consensus has yet been reached as to which of the different methods, the distribution-based or anchor-based method, should be preferred. This issue has been addressed before in other conditions. It is recommended to use both methods complementary to each other rather than separately with the resulting values narrowed down to a small range.[18 37] The distribution-based method provided higher scores than the anchor-based method. This finding has been reported before and is likely a result of the

distribution-based method using the statistical distribution of a heterogeneous population like chILD to calculate MIDs.[34 38]

In this study, we analysed data of children diagnosed according to current guidelines of the American Thoracic Society[27] and the European management platform for interstitial lung diseases in children.[28] Whereas those classification systems include a broad spectrum of diseases with different pathophysiological mechanisms, the clinical presentation and symptoms are very similar across this large patient group.[39] In contrast to adult ILD, the frequency of chILD is more than ten times lower and most of the diseases are extremely rare.[39] Although, splitting diseases into smaller entities is key for precision medicine, conducting randomised control trials for specific, some extremely rare diseases does not seem feasible. Therefore, we believe that using this 'basket approach' to calculate MIDs will help clinicians to interpret changes and scientists to better design RCTs.

As very recently done in interstitial lung diseases in adults, we selected results of lung function testing (FEV_1 and FVC) as appropriate anchors for this approach.[34] Of note, children under 5 years of age are usually not able to perform spirometry on an acceptable level. In consequence, one might argue that MIDs based on lung function data as anchor should not be used in infants. However, as the cooperation rather than any anatomical or structural issue, is preventing children under 5 years from performing acceptable spirometry manoeuvres, we argue that the anchor-based MIDs calculated in this study can be used across all age groups, particularly as we used age-independent z-scores of PFT results for this analysis.

Routine measurements of diffusion capacity for carbon monoxide (DLCO) for surveillance of fibrotic changes and disease progression is recommended in adult ILD.[40] This method provides a quantitative measure of gas transfer in the lungs defining respiratory status in patients with chronic lung diseases[41] and have been used as anchor to calculate MIDs in adult ILD.[34] However, as lung fibrosis in chILD is rarely seen,[42] DLCO in children is not widely used and current guidelines for chILD only recommend routine use for surveillance in children diagnosed with pulmonary haemorrhage.[43] As a result, only few DLCO data were entered into the register that are limited to children with pulmonary haemorrhage, and therefore, not used to calculate MIDs in this study.

For oxygen saturation in room air and respiratory rate (z-score) the distribution-based method revealed MIDs of 3.1% and 1.3, respectively. For these outcome parameters, we chose not to calculate the MIDs using the anchor-based method, as the statistical analysis did not find at least a moderate correlation between the scores and both anchors. For the Fan severity score, both methods were used. The MID ranged between 0.2 and 0.4. However, as only discrete changes of 1 or more on this 5-point severity illness scale are clinically meaningful, the MID for the Fan severity score may only be useful in changes of larger populations. As this illness score is chILD specific, no MIDs for the Fan severity score have been estimated in other respiratory conditions for comparison. The score is an independent measure of disease severity in chILD as it can be easily obtained across all age groups.

The MIDs for the HrQoL scores obtained in this study were consistent with published MIDs in other chronic conditions, ranging between 4% and 8%.[12 44] PROs provide a better understanding of the patients' perspectives regarding treatment benefits as well as health status and are therefore commonly used.[26] The multidimensional construct helps assessing the different components of well-being, and can therefore yield a more comprehensive description of the medical condition than the reporting of clinical symptoms.[45] The questionnaires are frequently used for monitoring of the subjective health status and as outcome parameter in clinical trials.[33 46 47] At the ceiling, however, the maximum possible improvement is limited and changes larger than the calculated MIDs might be needed for patients to be considered significant. A recent publication addressed this issue calculating MIDs for different degrees of disease severity across the same disease group. This allowed the authors to isolate the effects of the measures from the characteristics of the patients.[48] In this study, the MIDs calculated for different variables changed according to disease severity. However, the patient group with larger MIDs for one variable did not comprise patients with large MIDs for the other variable. The authors concluded that there is no need to specify different MIDs for different subgroups of patients and favoured a single MID for all patients. Nevertheless, conceptually for a rational use of MIDs a minimum level of disease severity must be present to perceive clinical improvement. Also, independent of the method used, MIDs represent a population average and might differ from individual patient's perception.

There are several limitations to consider when interpreting our findings. As no large randomised control trials in chILD exists, it was not possible to verify the MIDs calculated in this study. However, the response analysis that we performed was in

Table 4 Absolute change of vital signs and HrQoL scores across changes in FEV_1 and FVC between baseline and follow-up visit

	Deteriorated		Same		Improved	
Lung function change between visits	FEV_1<−1.64 (z-score)	FVC<−1.64 (z-score)	−1.64<FEV_1 < 1.64 (z-score)	−1.64<FVC < 1.64 (z-score)	FEV_1>1.64 (z-score)	FVC>1.64 (z-score)
Δ Fan severity score	−0.3	−0.3	0.2	0.0	0.7	0.4
Δ Health Status Questionnaire	−1.0	−1.0	0.7	0.8	2.7	2.0
Δ chILD-specific questionnaire	−12.2	−15.5	4.5	5.1	19.4	16.1
Δ Physical Health Summary score	−12.9	−14.5	3.7	3.6	21.5	18.2
Δ Psychosocial Health Summary score	−11.3	−13.3	2.5	3.4	12.7	12.8
Δ Total score	−12.1	−13.8	2.7	3.4	16.0	14.3

An absolute FEV1 and FVC z-score change of 1.64 between baseline and the follow upfollow-up visit was considered significant defining the groups 'deteriorated', 'same' and 'improved'.
chILD, childhood interstitial lung diseases; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HrQoL, health-related quality of life.

agreement with the MIDs calculated. Also, we used PFT data as anchor to calculate MIDs. For a comprehensive MID calculation it is recommended using additionally scale-based instruments that directly capture a patient's perception of well-being (eg, Visual Analogue Scale), data that we did not capture and therefore not included in this analysis.

A second limitation is that this is not a population-based study and chILD is a group of individually very rare conditions. Still, we were able to recruit a representative cohort over several years to calculate MIDs. Also, chILD is an umbrella term covering more than 200 different entities and diseases so rare that only a few patients have been reported. However, the uniform clinical presentation of respiratory disorders affecting lung parenchyma may justify this joint approach, which has recently been used to calculate MIDs in adult ILD.[34]

In this study, most variables were not normally distributed but skewed to one side, that is, more affected patients than healthy subjects were sampled. To overcome this issue, we calculated additionally anchor-based MIDs and used both methods in combination. Of note, the Kids Lung Register does not systematically assess why variables are not entered. It can only be speculated if PFT data were missed being recorded or participants were not able to perform spirometry for a certain reason (eg, due to sickness). However, for children able to perform spirometry on an acceptable level (older than 5 years) we did not find differences between participants with and without recorded PFT data regarding disease category or being symptomatic.

Also, participating centres were trained and provided with specific SOPs regarding how variables were to be collected. However, we did not monitor if data were collected as required according to the SOPs. The ceiling effect seen in HrQoL scores suggests that it may not be a sensitive measure in mild forms of the disease, and therefore, limited to monitor disease progression for such children. Similar results have been found in adult ILD calculating MIDs for HrQoL scores.[34] In this study, only parent HrQoL data were analysed as proxy for the children.

In summary, we used a cohort of patients with chILD to determine MIDs for respiratory rate (z-score), oxygen saturation in room air, Fan severity score and HrQoL scores using both distribution-based and anchor-based methods. The MIDs provided here will assist clinicians to monitor disease progression and help researchers to design RCTs in chILD.

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Contributors ES developed the theoretical framework, processed the analytic calculations, performed the data interpretation, and took the lead in writing the manuscript. MG designed and organised the project, organised the platform and contributed to the manuscript providing critical feedback. Clinical principal site investigators of the project were ES, MG, NS, JC, MW, NK, NE, JL and KK. All participating centres contributing less than 2% of the analysed data were listed under the chILD-EU collaborators group, which is included as a contributing author.

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