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Original Research

The minimal important difference of the constant work rate cycle test in severe COPD

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A B S T R A C T

Background: The Constant Work Rate Cycle Test (CWRT) is a commonly used and sensitive test to detect treatment success in patients with Chronic Obstructive Pulmonary Disease (COPD). Earlier, the Minimal Important Difference (MID) of the CWRT was estimated at 101 s (or 34%) change from baseline based on one well executed study. However, this study was performed in a population of patients with mild-to-moderate COPD, and we have learned that MIDs might be quite different in patients with severe COPD. Therefore, we aimed to establish the MID of the CWRT in patients with severe COPD.
Methods: We included 141 patients with severe COPD, who underwent either pulmonary rehabilitation, bronchoscopic lung volume reduction with endobronchial valves, or a sham bronchoscopy as a control group. CWRT workload was set at 75% of the peak work capacity, as determined by an incremental cycle test. We used the change in 6-min walking test (6-MWT), forced expiratory volume in 1s (FEV_1), residual volume (RV), and St. George's Respiratory Questionnaire (SGRQ) total score as anchors to calculate the MID.
Results: All anchors had an association of $\geq$0.41 with change in CWRT. The MID estimates for the different anchors were: 6-MWT 278 s (95%), FEV_1 273 s (90%), RV 240 s (84%), and SGRQ 208 s (71%). The average of these four MID estimates resulted in an MID of 250 s (or 85%).
Conclusion: We established the MID for CWRT at 250 s (or 85%) change from baseline in patients with severe COPD.

1. Introduction

Dyspnoea-limited exercise capacity is a key feature of patients with Chronic Obstructive Pulmonary Disease (COPD). Exercise capacity has been stated to reflect COPD severity more adequately than lung function parameters such as airflow limitation [1], and exercise capacity was determined to be the most important predictor of mortality in COPD [2]. Therefore, therapies in COPD often focus on improving exercise capacity [3]. Walking and cycling tests are commonly used to assess response to therapies, such as pulmonary rehabilitation or lung volume reduction treatments [4]. Although 6-min walking tests (6-MWT) are easy to administer [5], constant work rate cycle tests (CWRT) are more sensitive to detect treatment success in COPD [6,7].

Since not all statistically significant changes in outcome are clinically relevant for patients, minimal important differences (MID) are used to estimate treatment success. The MID can be defined as the smallest change in outcome that is perceived as beneficial by patients and is used amongst others to identify patients who are responders to therapy [8,9].

Based on one well executed study, the MID of the CWRT was earlier estimated at 101 s or 34% change from baseline in patients with COPD [10]. However, this study was performed in patients with mild-to-moderate COPD, and we have learned from earlier work that the MID for disease outcomes might be quite different in patients with severe COPD compared to patients with milder disease [11]. In this study, we aimed to establish the MID of the CWRT in patients with severe COPD.

2. Methods

2.1. Subjects and study design

We included data from two clinical trials in patients with severe COPD and hyperinflation: the SoLVE trial (NCT03474471) and EASE trial (NCT00391612) [12]. In the SoLVE trial, participants were randomized to either pulmonary rehabilitation or bronchoscopic lung volume reduction with endobronchial valves as initial treatment. In the EASE trial, patients were randomized in a 2:1 ratio to airway bypass or the control group, who underwent a sham bronchoscopy. For the EASE trial, data were used of the participants of the sham-control group. We excluded the airway bypass arm as a treatment group, since this

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treatment was not sustainable beneficial to patients (higher exacerbation rates and no differences in lung function, quality of life, or exercise capacity compared to the control group), and therefore not considered as an effective treatment [12].

Patients were included in our analysis if CWRT was performed at both baseline and follow-up. Follow-up visits were performed either within a week after completion of the pulmonary rehabilitation or two months after bronchoscopic lung volume reduction with endobronchial valves for participants of the SoLVE study, and after six months for the sham control group, since no CWRT was performed at the one- and three-month follow-up visits in the EASE trial. The trials were approved by the local ethics committees and all patients provided written informed consent.

2.2. Constant work rate cycle test (CWRT)

An incremental cycle test was performed prior to CWRT to determine peak work capacity. For the incremental cycle test, workload was increased with 5 or 10 Watt/minute according to the RAMP-protocol until a symptom-limited maximum was reached [13]. For CWRT, the workload was set at 75% of peak work capacity. Both cycle tests were performed on an electromagnetically braked cycle ergometer and patients were instructed to maintain a pedalling cadence of 60 rpm. Patients were encouraged to cycle for as long as possible. The test ended when the pedalling rate dropped below 55 rpm despite strong encouragement, or when the endurance time exceeded 500% of baseline at the follow-up visit in the SoLVE trial.

2.3. Six-minute walking test (6-MWT)

The 6-MWT was performed according to the ATS recommendations [5]. The test was administered in an enclosed corridor and patients were instructed to walk as far as possible in a 6-min time frame. In patients with severe COPD, an increase of 26 m is generally accepted as the MID [14].

2.4. Quality of life

Quality of life was assessed with use of the St. George's Respiratory Questionnaire (SGRQ) total score [15]. SGRQ scores range from 0 to 100, with lower scores representing a better quality of life. A decrease of 8 points (or −11.1%) is considered the MID in patients with severe COPD [11].

2.5. Pulmonary function tests

Spirometry and body plethysmography were performed according to ERS/ATS guidelines [16,17]. The MID of the forced expiratory volume in 1 s (FEV_1) is a decrease of 100 ml (or 12%) [18,19], and the MID for residual volume (RV) is a decrease of 400 ml (or −7.5%) in patients with severe COPD [20].

2.6. Statistical analysis

We calculated the absolute and relative changes from baseline to follow-up in CWRT and the anchor variables (6-MWT, SGRQ total score, FEV_1, and RV). We used the anchor-based method to estimate the MID. The anchor-based method relates changes in CWRT to changes in other variables with a known MID if an appreciable association is present. In line with previous studies, we included anchors with a correlation coefficient of ≥0.40 [11,20]. Spearman correlation coefficients were calculated to determine associations between the change in anchors and change in CWRT. For associations with an association of rho ≥0.40, linear regression analyses were performed with change in CWRT as dependent variable and change in anchor as independent variable. CWRT MIDs were estimated from the equations following linear regression analysis and the anchor MID. For the final MID calculation, we used the average of the MID estimates for the different anchors. All statistical analyses were performed with the use of SPSS (version 23, IBM, New York, USA), and P values below 0.05 were considered statistically significant.

3. Results

We included 141 patients who had CWRT measurements at both baseline and follow-up in our analyses. Patient characteristics at baseline are shown in Table 1. In our study population, 75 patients received a sham bronchoscopy and 66 patients were treated between baseline and follow-up (bronchoscopic lung volume reduction with endobronchial valves: n = 42, pulmonary rehabilitation: n = 24). Changes between baseline and follow-up are shown in Table 2 for patients of the sham bronchoscopy and treatment group.

3.1. MID estimates

We found significant associations between change in CWRT and all anchors with an association of rho ≥0.41. Scatter plots including Spearman correlation coefficients between change in CWRT versus change in 6-MWT, ΔFEV_1, ΔRV, and ΔSGRQ are shown in Fig. 1.

The MID estimates for the absolute change in CWRT from baseline were 278 s (6-MWT), 273 s (FEV_1), 240 s (RV), and 208 s (SGRQ) for the different anchors (Table 3), which resulted in an average MID of 250 s. The MID estimates for the relative change in CWRT from baseline were 95.1% (6-MWT), 90.7% (FEV_1), 84.5% (RV), and 71.9% (SGRQ), which resulted in an average MID of 85%.

4. Discussion

Our aim was to establish the MID of the CWRT in patients with severe COPD, as we hypothesized that the MID might be different in this patient group compared to patients with mild-to-moderate disease. Our study showed that the MID of the CWRT is 250 s (or 85%) in patients with severe COPD, which is higher than previously suggested MID values. To our knowledge, two studies have been performed to identify the MID of the CWRT in patients with COPD thus far [10,21]. In these studies, the MID was estimated at 101 s (or 34%) [10], and 100–200 s change from baseline [21], which are both lower than our established MID.

The difference in MID may be explained by our study population. Previously, it has already been demonstrated that the MID for the SGRQ is also higher in patients with severe COPD compared to those with a milder form of the disease, which might be due to the higher (*i.e.* worse)

Table 1
Patient characteristics at baseline.

	Baseline (n = 141)
Age, years	63.9 ± 7.5
Male, %	56.0
Pack years	49.1 ± 27.3
FEV_1, L	0.71 ± 0.22
FEV_1, % predicted	26.2 ± 8.0
FVC, L	2.40 ± 0.71
FVC, % predicted	69.4 ± 17.6
RV, L	5.17 ± 1.21
RV, % predicted	237.7 ± 48.0
RV/TLC ratio	0.66 ± 0.07
CWRT, sec	260 (196; 379)
6-MWT, m	310.9 ± 86.2
SGRQ, points	58.6 ± 13.0

Data are presented as mean ± SD or median (IQR). FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; RV = residual volume; CWRT = constant work rate cycle test; 6-MWT = 6-min walking test; SGRQ=St. George's Respiratory Questionnaire.

Table 2
Changes in CWRT and the anchor variables between baseline and follow-up for patients who underwent a sham bronchoscopy and patients who were treated with pulmonary rehabilitation or endobronchial valves.

	Sham bronchoscopy group (n = 75)	Treatment group (n = 66)
ΔFEV_1, L	−0.02 (±0.09)	0.14 (±0.20)
ΔRV, L	−0.02 (±0.52)	−0.59 (±0.75)
ΔSGRQ, points	−0.90 (±9.45)	−16.5 (±14.4)
Δ6-MWT, m	−13.2 (±51.7)	44.9 (±55.2)
ΔCWRT, sec	−51 (−170; 29)	296 (64; 968)
ΔCWRT, %	−22.2 (−54.7; 20.0)	127.8 (33.5; 340.5)

Data are presented as mean (±SD) or median (IQR). Δ: change compared to baseline; FEV_1 = forced expiratory volume in 1 s; RV = residual volume; SGRQ=St. George's Respiratory Questionnaire; 6-MWT = 6-min walking test; CWRT = constant work rate cycle test.

baseline scores [11]. Our study population consisted of patients with more severe COPD (mean FEV_1 = 26.2% of predicted vs. 45.0–46.8% of predicted), shorter 6-MWT distances (311 m vs. ±400 m), and worse quality of life scores (SGRQ = 58.6 points vs. 46.0 points) compared to the other MID studies [10,21]. In the earlier MID studies, mean cycle peak work capacities were found of 68 Watt and 89 Watt, respectively, while the mean peak work load of the SoLVE trial participants was 36 Watt (SD 18.2). Unfortunately, we were not able to obtain the peak workload data of the EASE trial participants. Our clinical experience is that cycling test with a lower workload are easier to improve than those with a higher workload, despite all incremental cycle tests being performed at maximum effort, and the associations we found between CWRT workload and change in CWRT endurance time in participants of the SoLVE trial provide support for this hypothesis (absolute change: rho = −0.24, p = 0.049; relative change: rho = −0.33, p = 0.006). Of note is that there are differences in baseline mean CWRT endurance time between our study and the two earlier studies (260 s vs. ±320 s [21] and 420 s [10]), although all mean values are in line with the guidelines, since workloads are recommended that result in baseline CWRT endurance times between 180 and 480 s [4].

Anther contributing factor to the difference found is the lack of a control group in both earlier studies [10,21]. In our study, we included a patient group who received a sham bronchoscopy as a placebo-controlled group, since MID estimates derived in trials that compare active treatments (without placebo or control group) may result in an underestimation of the treatment effect that is beneficial [22].

In our study, we used the multiple-anchor method for MID estimation. Anchor-based MID approaches are strongly dependent on the interrelationship between the anchor and the outcome measure. The most recent recommendations suggest a moderate to high association of ≥0.5 for an outcome measure to qualify as credible anchor in the single-anchor method [23], but single-anchor methods require higher associations than multiple-anchor methods to generate a valid MID [24]. Although there is no clear consensus on the required degree of association in a multiple-anchor method, associations of ≥0.30–0.35 have been recommended as acceptable associations [9]. In our study, all anchors had associations of ≥0.41 with our outcome measure (change in CWRT) and were therefore included in our analyses. We choose to use the average of the different anchor MID estimates for our MID calculation. Other considerations were the use of separate MIDs based on a Patient Oriented Evidence that Matters anchor (*i.e.* quality of life as measured by the SGRQ), and Disease Oriented Evidence anchors (*i.e.* FEV_1, RV, and 6-MWT). Based on the SGRQ, the MID would have been 208 s and slightly lower than the mean we calculated, but still considerably higher than the previously found MID in patients with mild-to-moderate disease. However, the SGRQ scores symptoms such as cough and phlegm as well, which might not necessarily reflect exercise tolerance [15]. Conversely, the use of Disease Oriented Evidence

Table 3
Constant work rate cycle test (CWRT) minimal important differences (MID).

	ΔCWRT		ΔCWRT %	
	MID	95% CI	MID	95% CI
6-MWT	278.7	170.7–386.4	95.1	64.1–126.0
FEV_1	273.7	135.6–411.8	90.7	54.4–127.0
RV	240.8	196.2–285.4	84.5	71.7–97.3
SGRQ	208.6	159.3–253.2	71.9	56.5–87.3
Average	250.5	218.5–282.4	85.6	75.7–95.5

Data are presented as seconds (95% CI) or percentage change (95% CI) from baseline. Δ: change compared to baseline; 6-MWT = 6-min walking test; FEV_1 = forced expiratory volume in 1 s; RV = residual volume; SGRQ=St. George's Respiratory Questionnaire.

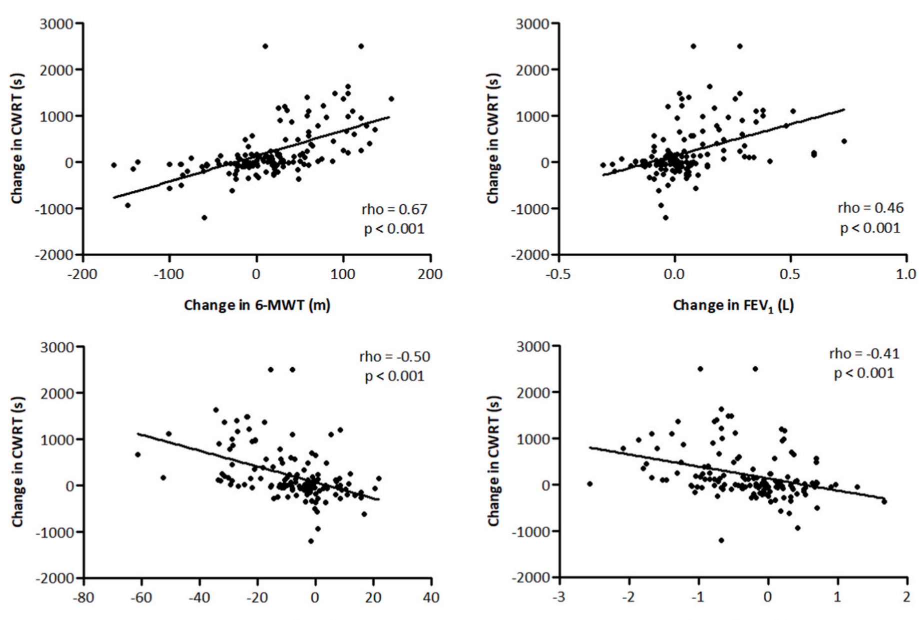

Fig. 1. Scatter plots of the 6-minute walking test (6-MWT), forced expiratory volume in 1 second (FEV1), St George's Respiratory Questionnaire (SGRQ) total score, and residual volume (RV) versus constant work rate cycle test (CWRT) endurance time at follow-up.

anchors would have resulted in an even higher mean of 264 s, but we believe that the combination of both type of anchors strengthens the applicability of the MID. We also considered the application of a weighted mean, but renounced this option given the arbitrary choices a weighted mean would entail.

Since the concept of an MID is to establish the smallest important difference, it is essential for an anchor-based MID to evaluate if the patient data compared on the anchor do not reflect a too large treatment effect rather than the minimal important treatment effect [23]. On the other hand, it is also a topic of debate in studies that assess MID according to the perceived treatment, whether the 'just detectable level of effect' of a treatment can be considered a clinically significant change [25]. In the study by Puente-Maestu et al. (a study that assessed MID according to the perceived improvement), the 'just detectable level of effect' was estimated at 101 s (95% CI: 86–116) or 34% (95% CI: 29–39) change from baseline. However, the mean change in CWRT endurance time was 512 s (95% CI: 472–571) or 121% (95% CI: 109–134) in the group who perceived their exercise capacity as 'better' [10], which is also substantially higher than our MID estimation.

In the study by Laviolette et al., a multiple-anchor approach was intended to be used for MID estimation [21]. However, no association was found between changes in 6-MWT and CWRT in that study, and only a modest association between changes in SGRQ and CWRT ($r = -0.31$, $p < 0.001$). Moreover, one year follow-up data was pooled with the data that was obtained directly following pulmonary rehabilitation in that study. Following linear regression analysis, an MID of 153 s (95% CI: 93–213) was found for a change of $\leq$ -4 units in SGRQ in that study, which is one of the earlier established MIDs for SGRQ in patients with COPD [26]. For our study, we used the MID for SGRQ in patients with severe COPD, which is established at a change of $\leq$ -8 units [11]. We found an MID of 140 s (95% CI: 67–213) in our study population if we applied a change of $\leq$ -4 units in SGRQ as well, which is fairly comparable to the results by Laviolette et al. However, this MID estimate is probably an underestimation for patients with severe COPD, since a higher MID of $\leq$ -8 units change has been established for this population [11].

Both earlier MID studies have been performed in patients who underwent a pulmonary rehabilitation program [10,21]. In COPD, many factors may limit exercise capacity directly or indirectly and different interventions may address different exercise limiting factors [27]. Exercise training in pulmonary rehabilitation may improve the muscle aerobic capacity, which delays the onset of metabolic acidosis and results in a later ventilatory limitation, whereas other interventions improve the ventilatory function (*i.e.* bronchodilators, bronchoscopic lung volume reduction interventions), or delay the onset of hypoxia-induced lactic acid production (supplemental oxygen therapy). But also anxiety and depression have been shown to influence exercise capacity, which is addressed in pulmonary rehabilitation [27].

Although treatment effect size may vary by disease severity, the MID should be applicable to any intervention from a theoretical point of view [22]. There are conflicting views in the literature on the advantages of a specific versus pan-intervention MID, but our ultimate choice of a pan-intervention MID was driven by the recognition that the reliability of an anchor-based MID is highly dependent on the degree of association between the anchors and the outcome measure. By selecting only patients from the SoLVE study (or patients who underwent BLVR), there would be only few non-responders, which significantly weakens the associations. Conversely, the group of participants from the EASE trial only contains few responders, which now results in a strong association between the anchors and outcome measure for the entire group. However, as discussed above, different interventions may sort dissimilar effects on the various anchors in a multiple-anchor approach, thus it might be hypothesized that an anchor-based MID obtained in one intervention group (*i.e.* pulmonary rehabilitation), does not directly translate to another (*i.e.* pharmacological interventions or lung volume reduction interventions) [28]. For example, in pulmonary rehabilitation patients learn to self-pace their walking speed, which may have a negative impact on the 6-MWT, but intense leg training has been shown to strongly improve submaximal endurance tests [29]. By including different treatments, we averaged different response patterns in order to estimate an MID that is applicable for multiple interventions in patients with severe COPD.

Our study has limitations. We included data from two clinical trials with different study end points, which resulted in the inclusion of follow-up data at two months for patients who underwent pulmonary rehabilitation or bronchoscopic lung volume reduction with endobronchial valves, and follow-up data at six months for patients of the placebo-controlled group who underwent a sham bronchoscopy. However, both follow-up durations can be considered short-term outcomes, and the optimal follow-up time varies by outcome and intervention [22]. We therefore believe that the benefits of an additional control group outweigh the limitation of different study endpoints.

In the SoLVE trial, the CWRT was ended when the endurance time exceeded 500% of baseline at the follow-up visit. In our study population, CWRT was stopped at 500% of baseline in nine patients, which might have led to a lower MID outcome.

As discussed above, we only assessed short-term outcomes in our study. Also both earlier MID studies studied the data directly following pulmonary rehabilitation [10], or pooled these with the one year follow-up data [21]. Due to the progressive nature of COPD, outcome measures may return to baseline values in more long-term follow-up ($\geq$1 year) as a result of disease progression, despite initial improvements following therapeutic interventions [22]. Consequently, the current MID could be less accurate for long-term follow-up.

A learning effect may be part of the MID estimate. One study that assessed the reliability of CWRT in patients with COPD, found a mean increase of 34 s if CWRT was repeated five days after the first CWRT, suggesting that a learning effect is present [30]. However, we found a median decline in CWRT of 51 s (IQR: 170; 29 s) at follow-up in our placebo-controlled group, which implies that this may not be applicable at more long-term follow-up or that the effect of progressive lung function decline in COPD exceeds the learning effect.

Finally, it should be noted that all included patients suffered from severe COPD with significant hyperinflation (defined as an RV >175% or predicted). Therefore, the results may not be directly applicable to patients whose severe COPD is characterized more by airway pathology. However, it is probable that the latter group has a limited exercise capacity with similar low workloads.

General considerations concern that MIDs evaluate the mean value of a population, which might not necessarily represent the threshold value for an individual patient as a result of the different values patients may place upon limitations they encounter in daily life [25]. MID estimates are above all useful in sample size calculations or to define the number of responders in clinical trials on a group level.

In conclusion, this is the first study to establish the MID of the CWRT in patients with severe COPD. We found an MID of 250 s (95% CI: 219–282 s) or 85% (95% CI: 75–95%) change from baseline. Future studies should focus on long-term follow-up data in this patient group and might be useful to confirm our results.

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CRediT authorship contribution statement

Marieke C. van der Molen: Conceptualization, Investigation, Formal analysis, Writing – original draft. **Dirk-Jan Slebos:** Funding acquisition, Conceptualization, Writing – review & editing. **Sonja W.S. Augustijn:** Investigation, Writing – review & editing. **Huib A.M. Kerstjens:** Conceptualization, Writing – review & editing. **Jorine E. Hartman:** Conceptualization, Writing – review & editing.

Declaration of competing interest

There is no conflict of interest.

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References

[1] T. Oga, K. Nishimura, M. Tsukino, S. Sato, T. Hajiro, Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status, Am. J. Respir. Crit. Care Med. 167 (4) (2003) 544–549, https://doi.org/10.1164/rccm.200206-583OC.

[2] M. Moll, D. Qiao, E.A. Regan, et al., Machine learning and prediction of all-cause mortality in COPD, Chest 158 (3) (2020) 952–964, https://doi.org/10.1016/j.chest.2020.02.079.

[3] D.M.G. Halpin, G.J. Criner, A. Papi, et al., Global initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD science committee report on COVID-19 and chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 203 (1) (2021) 24–36, https://doi.org/10.1164/rccm.202009-3533SO.

[4] L. Puente-Maestu, P. Palange, R. Casaburi, et al., Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement, Eur. Respir. J. 47 (2) (2016) 429–460, https://doi.org/10.1183/13993003.00745-2015.

[5] R.O. Crapo, R. Casaburi, A.L. Coates, et al., ATS statement: guidelines for the six-minute walk test, Am. J. Respir. Crit. Care Med. 166 (1) (2002) 111–117, https://doi.org/10.1164/ajrccm.166.1.at1102.

[6] T. Oga, K. Nishimura, M. Tsukino, T. Hajiro, A. Ikeda, T. Izumi, The effects of oxitropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. A comparison of three different exercise tests, Am. J. Respir. Crit. Care Med. 161 (6) (2000) 1897–1901, https://doi.org/10.1164/ajrccm.161.6.9905045.

[7] K.-C. Ong, W.-F. Chong, C. Soh, A. Earnest, Comparison of different exercise tests in assessing outcomes of pulmonary rehabilitation, Respir. Care 49 (12) (2004) 1498–1503.

[8] R. Jaeschke, J. Singer, G.H. Guyatt, Measurement of health status. Ascertaining the minimal clinically important difference, Contr. Clin. Trials 10 (4) (1989) 407–415, https://doi.org/10.1016/0197-2456(89)90005-6.

[9] D. Revicki, R.D. Hays, D. Cella, J. Sloan, Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes, J. Clin. Epidemiol. 61 (2) (2008) 102–109, https://doi.org/10.1016/j.jclinepi.2007.03.012.

[10] L. Puente-Maestu, F. Villar, J. de Miguel, et al., Clinical relevance of constant power exercise duration changes in COPD, Eur. Respir. J. 34 (2) (2009) 340–345, https://doi.org/10.1183/09031936.00078308.

[11] J.B.A. Welling, J.E. Hartman, N.H.T. Ten Hacken, K. Klooster, D.-J. Slebos, The minimal important difference for the St George's Respiratory Questionnaire in patients with severe COPD, Eur. Respir. J. 46 (6) (2015) 1598–1604, https://doi.org/10.1183/13993003.00535-2015.

[12] P.L. Shah, D.-J. Slebos, P.F.G. Cardoso, et al., Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial, Lancet (London, England) 378 (9795) (2011) 997–1005, https://doi.org/10.1016/S0140-6736(11)61050-7.

[13] T. Radtke, S. Crook, G. Kaltsakas, et al., ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases, Eur. Respir. Rev. 28 (154) (2019), 180101, https://doi.org/10.1183/16000617.0101-2018.

[14] M.A. Puhan, D. Chandra, Z. Mosenifar, et al., The minimal important difference of exercise tests in severe COPD, Eur. Respir. J. 37 (4) (2011) 784–790, https://doi.org/10.1183/09031936.00063810.

[15] P.W. Jones, F.H. Quirk, C.M. Baveystock, P. Littlejohns, A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire, Am. Rev. Respir. Dis. 145 (6) (1992) 1321–1327, https://doi.org/10.1164/ajrccm/145.6.1321.

[16] M.R. Miller, J. Hankinson, V. Brusasco, et al., Standardisation of spirometry, Eur. Respir. J. 26 (2) (2005) 319–338, https://doi.org/10.1183/09031936.05.00034805.

[17] J. Wanger, J.L. Clausen, A. Coates, et al., Standardisation of the measurement of lung volumes, Eur. Respir. J. 26 (3) (2005) 511–522, https://doi.org/10.1183/09031936.05.00035005.

[18] J.F. Donohue, Minimal clinically important differences in COPD lung function, COPD 2 (1) (2005) 111–124, https://doi.org/10.1081/copd-200053377.

[19] M. Cazzola, W. MacNee, F.J. Martinez, et al., Outcomes for COPD pharmacological trials: from lung function to biomarkers, Eur. Respir. J. 31 (2) (2008) 416–469, https://doi.org/10.1183/09031936.00099306.

[20] J.E. Hartman, N.H.T. ten Hacken, K. Klooster, H.M. Boezen, M.H.G. de Greef, D.-J. Slebos, The minimal important difference for residual volume in patients with severe emphysema, Eur. Respir. J. 40 (5) (2012) 1137–1141, https://doi.org/10.1183/09031936.00219111.

[21] L. Laviolette, J. Bourbeau, S. Bernard, et al., Assessing the impact of pulmonary rehabilitation on functional status in COPD, Thorax 63 (2) (2008) 115–121, https://doi.org/10.1136/thx.2006.076844.

[22] P.W. Jones, K.M. Beeh, K.R. Chapman, M. Decramer, D.A. Mahler, J.A. Wedzicha, Minimal clinically important differences in pharmacological trials, Am. J. Respir. Crit. Care Med. 189 (3) (2014) 250–255, https://doi.org/10.1164/rccm.201310-1863PP.

[23] T. Devji, A. Carrasco-Labra, A. Qasim, et al., Evaluating the credibility of anchor based estimates of minimal important differences for patient reported outcomes: instrument development and reliability study, BMJ 369 (6) (2020), m1714, https://doi.org/10.1136/bmj.m1714.

[24] G.H. Guyatt, D. Osoba, A.W. Wu, K.W. Wyrwich, G.R. Norman, Methods to explain the clinical significance of health status measures, Mayo Clin. Proc. 77 (4) (2002) 371–383, https://doi.org/10.4065/77.4.371.

[25] P.W. Jones, Interpreting thresholds for a clinically significant change in health status in asthma and COPD, Eur. Respir. J. 19 (3) (2002), https://doi.org/10.1183/09031936.02.00063702, 398 LP - 404.

[26] P.W. Jones, St. George's respiratory Questionnaire: MCID, COPD 2 (1) (2005) 75–79, https://doi.org/10.1081/copd-200050513.

[27] M.A. Spruit, S.J. Singh, C. Garvey, et al., An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation, Am. J. Respir. Crit. Care Med. 188 (8) (2013) e13–e64, https://doi.org/10.1164/rccm.201309-1634ST.

[28] T. Troosters, How important is a minimal difference? Eur. Respir. J. 37 (4) (2011) 755–756, https://doi.org/10.1183/09031936.00156410.

[29] L. Puente-Maestu, M.L. Sánz, P. Sánz, J.M. Cubillo, J. Mayol, R. Casaburi, Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease, Eur. Respir. J. 15 (3) (2000) 517–525, https://doi.org/10.1034/j.1399-3003.2000.15.15.x.

[30] D.E. O'Donnell, J. Travers, K.A. Webb, et al., Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD, Eur. Respir. J. 34 (4) (2009), https://doi.org/10.1183/09031936.00168708, 866 LP - 874.