Minimal clinically important differences in average, best, worst and current intensity and unpleasantness of chronic breathlessness

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This cohort study determined clinically important differences for current intensity and unpleasantness and the average, best and worst intensity of the past 24 h of chronic breathlessness, which is important for the design of therapeutic trials https://bit.ly/3amslls

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ABSTRACT

Background: Chronic breathlessness has devastating consequences. The minimal clinically important difference (MCID) for current intensity has been estimated as 9 mm on a 100-mm visual analogue scale (VAS). We aimed to determine MCIDs for commonly used dimensions and recall periods: the current unpleasantness and current, average, best and worst intensity of the past 24 h for chronic breathlessness.

Methods: This was a secondary analysis of a randomised controlled trial of morphine versus placebo over 7 days in people with chronic breathlessness from severe disease. The breathlessness scores were self-reported using a diary each evening on 100-mm VAS. The MCID for improvement in each score was estimated using anchor-based and distribution-based methods.

Results: 283 participants (mean age 74.2 years; 63% male; 58% COPD; 87.0% modified Medical Research Council (mMRC) score 3–4) were included. Anchor-based MCIDs for breathlessness scores ranged from −13.9 mm to −9.5 mm. The MCIDs were similar when using different anchors and across all participants, and participants with more severe breathlessness (mMRC 3–4). Distribution-based effect sizes were classed as small (−4.7–6.3 mm), moderate (−9.4–12.5 mm) and large (−15.0–20.0 mm) effect. Sample sizes for trials using the different scores were proposed. MCIDs of absolute change were more stable than using relative change from baseline.

Conclusion: An improvement of ∼10 mm on a 100-mm VAS is likely to be clinically meaningful across commonly used measures of chronic breathlessness (current intensity, unpleasantness, and average, best and worst intensity over the past 24 h) to evaluate clinical benefit and effects in therapeutic trials.
Introduction
Chronic breathlessness [1] is a key cause of suffering in advanced disease [2]. Subjective sensations of intensity and unpleasantness may be discerned as distinct aspects by individuals and their impact experienced within the context of duration of the symptom (acute versus chronic) and the meaning attributed by the person. Breathlessness should be measured in routine care as an essential part of disease evaluation to guide best management [3–5]. Although chronic breathlessness cannot be encapsulated in a single quantitative measure [6], higher scores in unidimensional breathlessness scores do predict adverse clinical outcomes and can demonstrate change in response to an intervention, and thus are relevant for patient care and in clinical trials [7].

Different breathlessness dimensions and recall periods have been used and assessed in trials since a consensus statement on the measurement of breathlessness in advanced disease [5], including the current intensity (or severity), current unpleasantness, and the average, best or worst intensity during the past 24 h [7–15].

The minimal clinically important difference (MCID), defined as the smallest change that is meaningful to the patient, is a key concept for determining the clinical relevance of effects in therapeutic trials [16]. Data are limited on MCIDs for measures of chronic breathlessness [7]. Using an individual pooled data analysis (n=213) of current breathlessness intensity from three trials [17–19] and one dose titration study [20], Johnson et al. [7] reported a MCID for current intensity of chronic breathlessness of 9 mm on a 100-mm visual analogue scale (VAS) using both participant-anchored and distribution-based methods. Distribution-based effect sizes were 5.5 mm for small, 11.3 mm for moderate and 18.2 mm for large effect [7]. The absolute MCID, based on absolute change from baseline was found to be more stable compared with the relative MCID (which is based on percentage change from baseline), and absolute MCIDs were therefore concluded to be preferable for use in trials [21].

However, we do not know the MCIDs of chronic breathlessness for different frequently used dimensions and temporal periods: current unpleasantness, and the average, best and worst intensity during the past 24 h [22]. For example, measures of “current breathlessness” and “usual breathlessness” correlate poorly and probably represent different constructs [23], and so may have different MCIDs. Furthermore, it is not known whether MCIDs differ by underlying diagnosis (most data pertain to COPD) as seen in (acute) pain [24], or in patients with worse activity limitation due to breathlessness, as measured using the modified Medical Research Council (mMRC) scale [22, 25]. This knowledge is of fundamental importance for choosing unidimensional assessment scales to reflect patients’ experiences in clinical practice and trials.

The primary aim of this paper was to determine MCIDs for improvement in current breathlessness intensity and unpleasantness, and for the average, best and worst intensity during the past 24 h in participants with advanced disease and chronic breathlessness. Secondary aims were to evaluate MCIDs separately in participants with more severe breathlessness (mMRC 3–4).

Methods
Study design and population
This is a secondary analysis of a randomised, parallel arm, multi-site, fixed dose, placebo controlled, phase III trial of 20 mg extended release morphine daily placebo for 7 days in patients with chronic breathlessness (Australian New Zealand Clinical Trials Registry, ACTRN12609000806268). The main analysis found no difference in breathlessness between the trial arms when measuring “breathlessness now” [14]. The database was previously used to evaluate agreement between breathlessness severity and unpleasantness [12], to compare mMRC ratings between clinicians and participants [26] and to evaluate treatment-adverse events [27].

Participants were recruited from 14 respiratory and palliative care services across Australia in the Australian Government funded national Palliative Care Clinical Studies Collaborative [14]. The main eligibility criteria were age ≥18 years; chronic breathlessness defined as mMRC [28] breathlessness score ≥2 at screening despite optimal management of underlying cause(s) of breathlessness; stable breathlessness medications for the previous week except “as needed” medications; an Australia-modified Karnofsky Performance Status (AKPS) score ≥40 [29]; expected survival ≥2 months; and ability to complete a daily diary [14].

Ethical considerations
The trial was approved by the Southern Adelaide Clinical Research Ethics Committee (Dnr: EC00188) and the local ethics committee at each site prior to first recruitment at each site. All participants gave their informed written consent to participate and the trial was monitored in accordance with good clinical practice [30].
Assessments
The mMRC breathlessness scale [25] and function using the AKPS were rated by the physician at eligibility screening [26]. Other baseline assessments are described elsewhere [14]. Breathlessness scores were rated by participants using 100-mm VAS in a diary each evening (current intensity, current unpleasantness, and worst, best and average intensity during the past 24 h) at baseline and for the 7 days of intervention (low-dose morphine or placebo). The VAS is a reliable and valid scale for unidimensional measurement of breathlessness [31, 32]. Current intensity was assessed using the question "How is your breathlessness right now?" between 0 ("None") and 100 ("Worst possible"). Current unpleasantness was then assessed using the question "Right now how would you rate the unpleasantness of your breathlessness?" between 0 ("None") and 100 ("The most unpleasant I have ever felt"). The participant was then asked to rate the average, best and worst intensity of breathlessness during the past 24 h using similar scales as the current intensity.

At the end of the study, participants were asked (double-blinded) whether they had "been less breathless during the past week" ("less breathlessness") and "this medication would benefit me enough to be on it long term" ("benefit"), which were used in this current analysis as anchors for determining a participant-defined clinically meaningful change in breathlessness during the study week. The anchors were used in line with recommendations to evaluate MCIDs across several anchors and methods [16] and as the questions related to the key concept of a MCID, to measure a change in breathlessness that would be clinically important in terms of patients' experiences and treatment decisions.

Statistical analyses
Participant baseline characteristics were summarised by descriptive statistics. For each breathlessness score (current unpleasantness and current, average, best and worst intensity), imputation was performed for those with 1) missing baseline measurements, which was imputed as their first-day measurement; and 2) missing day 7 measurements, which was imputed as the last available value for each score at day 5 or 6 [14]. Sensitivity analysis without any imputation was firstly performed. We then imputed the missing values using multiple imputation approach (imputation model set as multivariate normal regression adjusting for baseline characteristic factors; with 20 imputations per case). Both sensitivity analyses yielded similar results as the main analysis.

MCIDs were calculated using anchor-based methods as recommended [16, 33]. The "less breathless" and "benefit" questions were used as participant anchors of breathlessness change. MCIDs were calculated as the change from baseline to day 7, in the group who affirmed the anchor question (response) compared with the group who did not affirm the question (nonresponse) for each breathlessness scores with each of the two anchors. The estimates were reported with 95% confidence intervals. For each breathlessness score, MCIDs were calculated for all participants and separately for the subgroups with more severe breathlessness (mMRC 3–4).

Distribution-based methods were used to further explore the differences in the scores. The baseline standard deviations of 0.25, 0.5 and 0.8, respectively, were used to define small, medium and large effects [7]. Standard error of measurement [32], defined as the baseline standard deviation multiplied by the square root of 1 minus sample test–retest reliability coefficient, were also calculated for comparison purpose. One standard error of measurement can be regarded as an estimate of the MCID [34]. Sample sizes required to detect a MCID change in each breathlessness score with assumed common baseline standard deviation, 90% power (typically used in definitive trials) and a two-sided $\alpha=0.05$ were calculated using nQuery (version 8.4; Statistical Solutions, Boston, MA, USA). Stata (version 15.1; StataCorp, College Station, TX, USA) and R (version 3.5; www.r-project.org) were used for the other statistical analyses.

Relative MCIDs using anchor-based methods, defined as a change divided by the score at baseline, were calculated for comparison with the absolute MCIDs (main analysis) [21].

Results
Out of 284 randomised participants, 283 participants (one randomised participant did not meet the inclusion criteria of "prognosis of ≥2 months in the opinion of the treating clinician") were included for analysis: mean±SD age 74.2±9.3 years; 63.2% male; mean±SD AKPS 61.2±10.5; main diagnoses COPD (58.0%) and cancer (16.6%); and 87.0% had a mMRC of 3–4 (table 1).

Anchor-based MCIDs for improvement in the breathlessness scores for the study population ranged from 9.5 mm to 13.9 mm (figure 1). The MCIDs were similar when using the two different participant anchors, as shown by the largely overlapping 95% confidence intervals (supplementary table S1). In addition, the
estimates were largely similar to the main analysis for subgroup analyses in people with mMRC 3–4 (supplementary table S2).

Using distribution-based methods, the MCIDs were consistent with small-to-moderate changes. A small change ranged between 4.7 and 6.3 mm; moderate change between 9.4 and 12.5 mm; and large change between 15.0 and 20.0 mm (table 2). The standard error of measurements for breathlessness ranged from 9.7 to 16.4, slightly higher than the MCIDs calculated by the anchor-based approach.

Sample sizes required to detect a current MCID’s change in each breathlessness score (90% power and \( \alpha = 0.05 \)) are shown in table 3. The relative MCIDs ranged from \(-26.9\%\) to \(-73.5\%\) and varied more between the breathlessness scores than the absolute MCIDs (supplementary table S3).

Discussion
This study for the first time establishes MCIDs for improvement in a range of commonly used measures of chronic breathlessness: the current intensity and unpleasantness, and the average, best and worst intensity over the past 24 h. These novel data are important to help interpret symptom response in clinical practice and for valid measurement in interventional trials. Sample size estimations are presented and compared between the measures.

The anchor-based MCIDs ranged from 9.5 mm to 13.9 mm, which is slightly higher than the previous estimate of 9 mm (95% CI 2.1–15.8) for current breathlessness [7]. However, the present 95% confidence intervals overlapped with the earlier estimate [7]. In the present analysis, MCIDs were similar when calculated using two different participant anchors and were consistent with distribution-based estimates, which supports the validity of the present findings. Another novel finding is that MCIDs were similar to in the whole population for participants with more severe breathlessness (mMRC 3–4). Consistent with the previous analysis by JOHNSON et al. [21], MCIDs for absolute change were more stable and reliable than the relative MCID (relative change compared to baseline). Thus, this study confirms that treatment effect should be evaluated using the absolute MCID. Sample sizes (using the present anchor-based MCIDs) were calculated for a definite trial (using 90% power and \( \alpha = 0.05 \)) and ranged between 61 and 143 participants for different breathlessness scores. Sample sizes were similar in participants with mMRC 3–4. Some previous research suggests that 1 SEM is equivalent to MCID [34]. In the present analysis, standard errors of measurement were consistent with the anchor-based estimates, supporting the use of 1 SEM to estimate the MCID.

### Table 1 Baseline characteristics

| Subjects | 283 |
|----------|-----|
| Age years | 74.2±9.3 (44.3–94.1) |
| Female | 104 (36.8) |
| Performance status (AKPS) |  |  |
| 61.2±10.5 (3–90) |
| BMI kg·m\(^{-2}\) | 25.5±7.3 (12.3–66.1) |
| mMRC breathlessness score at baseline rated by clinician |  |  |
| 2 | 22 (7.8) |
| 3 | 140 (49.5) |
| 4 | 106 (37.5) |
| Missing | 15 (5.3) |
| Primary cause of breathlessness |  |  |
| COPD | 164 (58.0) |
| Cancer | 47 (16.6) |
| Cardiac failure | 4 (1.4) |
| Mixed | 37 (13.1) |
| Other | 31 (11.0) |
| Charlson Comorbidity Index | 3.3±2.5 (0–13) |
| Oxygen use | 161 (56.9) |
| Smoking status |  |  |
| Never-smoker | 49 (17.3) |
| Ex-smoker | 199 (70.3) |
| Current smoker | 33 (11.7) |
| Missing | 2 (0.7) |

Data are presented as n, mean±SD (range) or n [%]. AKPS: Australia-modified Karnofsky Performance Status; BMI: body mass index; mMRC: modified Medical Research Council scale.

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When using a MCID, it should be remembered that while the estimated mean change for the population is likely to be clinically significant for the individual [16], there is always a degree of uncertainty around the true MCID for the individual. This uncertainty is reflected in the present analysis by the confidence intervals, which were largely overlapping between the compared measures and groups. Taken together, the present findings support an MCID for the different measures of chronic breathlessness ∼10 mm on a 100-mm VAS (figure 1).

Strengths of the present analysis include that it is based on the largest randomised controlled trial of chronic breathlessness to date, with self-reported breathlessness scores at similar time points daily over 1 week. MCIDs were evaluated using two different participant anchors and distribution-based methods, as recommended [16].
Several potential limitations should be noted. It could be argued that the present estimates may not reflect the minimal important differences, as “minimal” was not included in the anchors. We used available anchors that were considered to relate to a difference that was clinically important (“I have been less breathless during the past week” and “This medication would benefit me enough to be on it long term”). While the true minimal important differences may be slightly smaller, the present estimates are supported by the distribution-based analysis that they represent small to moderate effect sizes. Subgroups were too small to evaluate MCIDs in mMRC \(\leq 2\) and in younger patients, which should be investigated in analyses of pooled trial data. As participants were not specifically instructed on the difference between intensity and unpleasantness, the meaning of the upper scale anchors and the ratings could be conflated between intensity and unpleasantness for some participants. The present MCIDs pertain mainly to improvement in breathlessness and cannot be assumed to apply also to deterioration in breathlessness. However, benefit is the most relevant for use in clinics and therapeutic trials.

These findings have several important implications: a change of 10 mm on a 100-mm VAS (or one unit on a 0–10 numerical rating scale) is likely to represent a change in chronic breathlessness that is clinically relevant or meaningful for the participant sufficient to inform clinical practice. MCIDs for different breathlessness dimensions and recall periods are given. When designing clinical trials, the use of an

### TABLE 2 Distribution-based analysis of clinically important differences in different breathlessness measures

|                | Unpleasantness | Intensity |
|----------------|----------------|-----------|
|                | Current | Current | Average | Best | Worst |
| **Change**     |         |         |         |      |       |
| Small (0.25 SD baseline) | 6.1    | 6.3     | 4.7     | 5.4  | 6.0   |
| Moderate (0.5 SD baseline) | 12.2   | 12.5    | 9.4     | 10.8 | 12.0  |
| Large (0.8 SD baseline)  | 19.5    | 20.0    | 15.0    | 17.3 | 19.1  |
| **Standard error of measurement** | 14.6 | 16.4 | 9.7 | 12.2 | 14.9 |

Estimates are mm on a 100-mm visual analogue scale.

### TABLE 3 Sample sizes for breathlessness scores using participant-anchored minimal clinically important differences (MCIDs) for each breathlessness score as mean difference and common baseline standard deviation, at 5% two-sided significant level and 90% power

|                | Unpleasantness | Intensity |
|----------------|----------------|-----------|
|                | Current | Current | Average | Best | Worst |
| **"I have been less breathless during the past week"** |         |         |         |      |       |
| All            |         |         |         |      |       |
| MCID           | −10.9   | −13.9   | −9.5    | −12.4 | −10.9 |
| Baseline SD    | 25.1    | 24.4    | 19.8    | 21.3  | 24.3  |
| Sample size n  | 113     | 66      | 92      | 63    | 106   |
| mMRC 3,4       |         |         |         |      |       |
| MCID           | −10.7   | −14.5   | −8.7    | −12.7 | −11.1 |
| Baseline SD    | 24.5    | 24.5    | 19.7    | 21.2  | 24.4  |
| Sample size n  | 112     | 61      | 109     | 60    | 103   |
| **"This medication would benefit me enough to be on it long term"** |         |         |         |      |       |
| All            |         |         |         |      |       |
| MCID           | −10.2   | −9.9    | −11.4   | −12.2 | −11.3 |
| Baseline SD    | 26.5    | 24.4    | 19.7    | 21.2  | 24.3  |
| Sample size n  | 143     | 129     | 64      | 65    | 99    |
| mMRC 3,4       |         |         |         |      |       |
| MCID           | −10.1   | −9.5    | −10.9   | −13.0 | −11.4 |
| Baseline SD    | 24.5    | 24.4    | 19.7    | 21.2  | 24.4  |
| Sample size n  | 125     | 140     | 70      | 57    | 98    |

mMRC: modified Medical Research Council scale.

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absolute MCID is preferred (over relative), and sample sizes are suggested for the different measures of chronic breathlessness. Further research is needed on MCIDs of acute-on-chronic breathlessness, MCIDs for symptom improvement versus worsening and how the MCID is influenced by factors including the baseline severity and history of chronic breathlessness.

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