A ‘CALL TO ACTION’ IN DETERMINING AND ESTIMATING A MINIMUM IMPORTANT DIFFERENCE (MID) IN 6-MINUTE WALKING DISTANCE (6MWD) IN PH-ILD

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1. INTRODUCTION AND OBJECTIVE

People with pulmonary hypertension (PH) associated with interstitial lung disease (PH-ILD) report reduced exercise capacity, impaired quality of life and worse survival outcomes [1, 2]. The condition is progressive, and management includes supportive therapies such as supplying oxygen, diuretics and pulmonary rehabilitation [3]. Due to its pathophysiologic overlap with pulmonary arterial hypertension (PAH), clinical trials have evaluated the efficacy of vasodilatory therapies for PH-ILD [4]. The INCREASE (NCT02630316) trial reported beneficial outcomes for those receiving treatment, with patients displaying improved long-term overall survival and six-minute walking distance (6MWD) [1].

A challenge of examining patient outcomes in clinical trials is determining if the observed differences constitute a clinically meaningful change for the patient. The minimal important difference (MID) of an outcome refers to the smallest difference in an outcome that patients can perceive as meaningful, requiring a change in their management. Previous work has established MID estimates for the 6MWD of people with PAH and chronic respiratory conditions [5-7]. However, there are currently no PH-ILD-specific estimates, and given the comparatively reduced exercise capacity, existing estimates for PAH may not be representative. This study sought to use different analytical methods and structured expert elicitation (SEE) to generate plausible MID estimates to inform interpretations of patient outcomes in clinical trials for PH-ILD-specific therapies.

Objective: Generate MID estimates for the 6MWD of people with PH-ILD by (1) analyse individual patient-level data from the INCREASE trial and (2) eliciting clinical expert judgements.

2. METHODS

INCREASE TRIAL ANALYSIS

Two distributional approaches were used: effect size (ES) and standardized response mean (SRM). Replicating previous studies defining the MID as the change in scores corresponding to a ‘small’ ES threshold, the MID was computed as the baseline standard deviation (SD) multiplied by 0.2 (1) [8].

$$MID_{ES} = \sigma_{baseline} * 0.2 \quad (1)$$

Previous work estimating the MID for the 6MWD of people with PAH and chronic obstructive pulmonary disorder (COPD) using the SRM approach applied a threshold of 0.5 SDs [7]. Thus, the MID was computed as the SD of change (from baseline to week 16) multiplied by 0.5 (2).

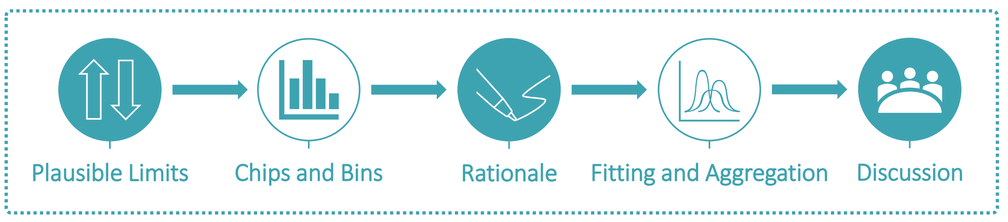
$$MID_{SRM} = \sigma_{change} * 0.5 \quad (2)$$

The intervention arm outcomes informed the calculations, rather than the between-arm difference, as the estimates were intended to represent a clinical change independent of the placebo effect. A follow-up responder analysis was conducted to assess the proportion of patients achieving an improvement in 6MWD corresponding with the MID estimates. Subgroup analyses designating individuals (in both arms) as “improved” (> 0 m) or “no change/deterioration” (≤ 0 m) based on the change in 6MWD between baseline and week 16 were also conducted. These analyses were subject to identical distributional methods.

STRUCTURED EXPERT ELICITATION

More information concerning the design, preparation and implementation of the SEE workshop are presented in an adjoining poster (SA5). A summary of our approach is provided below.

The Medical Research Council (MRC) protocol and associated SEE resources (STEER) were implemented [9, 10]. The materials were piloted by experts independent of the study sample before implementation and were distributed one week before the workshop. Pulmonologists and respiratory physicians (N = 5) from the United Kingdom and Germany participated.



Responses were fit to a suitable parametric distribution via least squares estimation, and an aggregate distribution was generated via linear opinion pooling. The MID was computed as the expected value of the pooled distributions. The fitted distributions were displayed during facilitated group discussions to examine between-expert variability. The experts were allowed to alter their distributions post-discussion.

3. RESULTS

INCREASE TRIAL ANALYSIS

An improvement in 6MWD was observed in the inhaled treprostinil arm (*n* = 130), while those receiving a placebo (*n* = 128) displayed reduced exercise capacity between time points. The observed mean difference in 6MWD between arms was +29.5 m ($p < 0.05$) (Table 1).

The ES and SRM analyses yielded estimates of 25.8 m and 19.8 m, respectively (Table 2). The subgroup analyses revealed estimates ranging between 18.7 m and 24.7 m; a consistent score of approximately 19 m was observed.

The responder analysis revealed a higher proportion of people receiving treatment achieved an improvement of at least 20 m (49% vs 31%), 26 m (45% vs 26%) and 30 m (40% vs 26%) at week 16 ($p < 0.05$) between timepoints (Figure 1).

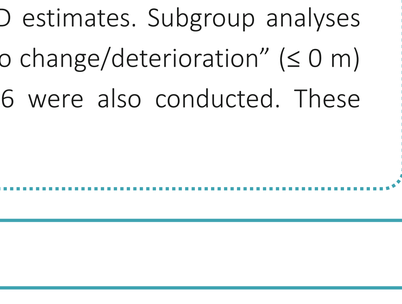
TABLE 1

Parameter	In. Treprostinil (*n* = 130)	Placebo (*n* = 128)	Treatment Effect (95% CI)
Baseline 6MWD (m), mean (SD)	257.0 (99.1)	272.6 (90.1)	
Week 16 6MWD (m), mean (SD)	278.1 (97.4)	264.2 (111.3)	
6MWD Δ (m), mean (SD)	+ 21.1 (51.6)	- 8.4 (67.5)	+ 29.5 (14.7 – 44.2)*

TABLE 2

Distributional Approach	Standard Deviation	Threshold	MID (m)
Effect size	99.1	0.2 SD	19.8
Standardised response mean	51.6	0.5 SD	25.8

FIGURE 1



The dotted vertical lines on the cumulative density function indicate the 20 m (left) and 30 m (right) thresholds. The central solid vertical line indicates the 26 m threshold.

STRUCTURED EXPERT ELICITATION

The expected value of the fitted distributions for the pre-discussion responses ranged between 17.5 m (SD = 1.4 m) and 47.1 m (SD = 11.8 m) and was 31.9 m (SD = 12.4 m) for the pooled distribution (Figure 2). For the post-discussion task, the expected value ranged between 24.8 m (SD = 2.0 m) and 40.6 m (SD = 8.7 m) and was 31.0 m (SD = 12.4 m) for the pooled distribution (Figure 2).

The group discussions and rationale statements revealed that the experts had based their responses on their clinical experience, what they perceived as clinically meaningful for patients and existing data for PAH populations. Multiple experts indicated that the MID for PH-ILD should be moderately lower than that reported for PAH, noting the reduced exercise capacity observed in this population.

A post hoc scenario analysis was conducted, excluding one response owing to task comprehension concerns due to contradictory statements present in the expert’s rationale statements. The expected value of the pooled distribution in the scenario was 28.6 m (SD = 6.9 m).

FIGURE 2

4. CONCLUSIONS

Multiple plausible PH-ILD-specific MID estimates were generated, ranging between 18.7 m and 31.0 m. These values fell below those demonstrated in PAH populations (approximately 33 m). The findings provide a foundation for interpreting clinical trials for PH-ILD-specific therapies. Further work is required to supplement our results, for instance, by applying anchor-based methods using validated patient-reported outcome measures. The distributional techniques used are also sample-specific and influenced by variability. Alternative approaches based on the measurement precision of the instrument should be implemented to elucidate meaningful change applicable across samples.

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