Development and Validation of a Conceptual Model to Inform the Cost Effectiveness of Inhaled Treprostinil for PH-ILD

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1. CONTEXT & OBJECTIVES

Pulmonary hypertension associated with interstitial lung disease (PH-ILD) is a rare and severe disease associated with frequent disease exacerbations, reduced health-related quality of life, and poor survival. PH-ILD has a substantial disease burden and is categorised as Group 3 in the World Health Organisation (WHO) pulmonary hypertension (PH) classification system. No cost-effectiveness models for PH-ILD treatments have been published.

The safety and efficacy of inhaled treprostinil has been investigated in the 16-week INCREASE randomised control trial (NCT02630316)[1] and open-label extension (OLE) (with a maximum length of 108 weeks) (NCT02633293).[2] The primary end point of the randomised control trial was the difference between the two groups in the change in peak 6-minute walk distance (6MWD) from baseline to week 16. The trials demonstrated that inhaled treprostinil improved the 6MWD in people with PH-ILD: the least squares mean difference in peak 6MWD from baseline and 16 weeks between the inhaled treprostinil and placebo group was significant (31.12m; P<0.001). [1] Other key outcome measures in both trials, used to determine overall survival and time to clinical worsening, included forced vital capacity (FVC%), acute lung-disease exacerbations, cardiopulmonary hospitalisations and lung transplants. Clinical worsening occurred in 22.7% and 33.1% of people in the inhaled treprostinil and placebo arms respectively over the 16-week trial follow-up period (hazard ratio, 0.61; 95% confidence interval, 0.40 to 0.92; P = 0.04).[1]

Objective: To conceptualise and validate a de novo economic model for PH-ILD that appropriately captures both the progressive nature of the disease and the effectiveness of inhaled treprostinil, informed by the key outcome measures in the INCREASE trial.

2. METHODS

The de-novo model conceptualisation was informed by a targeted literature review, as well as consideration of both the INCREASE outcome measures and external natural history data sources. As the targeted literature review identified zero previously published models in PH-ILD, models related to pulmonary hypertension or interstitial lung disease were also reviewed. Validation was completed through individual interviews and advisory boards with three clinical and two health-economic experts.

3. RESULTS

Key Considerations

The first stage of the model conceptualisation process was to determine if there were any categories in the clinical management of PH-ILD that could be directly used to inform the health states of the cost-effectiveness model.

No PH-ILD-specific staging systems were identified within the targeted literature review, nor raised in clinician interviews. As the INCREASE trial outcomes were not directly applicable, it was considered inappropriate to use the outcomes within an established single disease severity classification system in a related condition. Therefore, the adaptation of a pulmonary arterial hypertension risk assessment tool was considered. The risk assessment tool published by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) could have been used to separate the prognosis (estimated as one-year mortality) of people with PH-ILD into three categories (low, intermediate and high risk) using outcomes including WHO functional class, 6MWD, cardiopulmonary exercise testing and imaging.[3]

Ultimately, it was not possible to use any of the risk stratification systems directly within the model because at least one clinical variable used in each system, in particular the WHO functional class, was not collected within the INCREASE trial. Additionally, the application of these systems are not necessarily considered standard practice. Clinical experts also advised against using either a truncated version (excluding variables) or attempting to transform the trial endpoints to match the classification system.

The clinical experts stressed the importance of using the change in 6MWD and FVC to capture the decline in PH and ILD, respectively. None of the risk stratification systems incorporated both of these outcome measures and, therefore, it would have been necessary to create a new, unvalidated, stratification system. The experts at both advisory boards recommended that published, routinely used and validated thresholds specific to PH-ILD should be used to define any risk stratifications (as opposed to PH- or ILD-specific thresholds). Furthermore, it would not have been possible to use risk stratification systems without the conversion of data from the INCREASE trial. Therefore, this option was excluded.

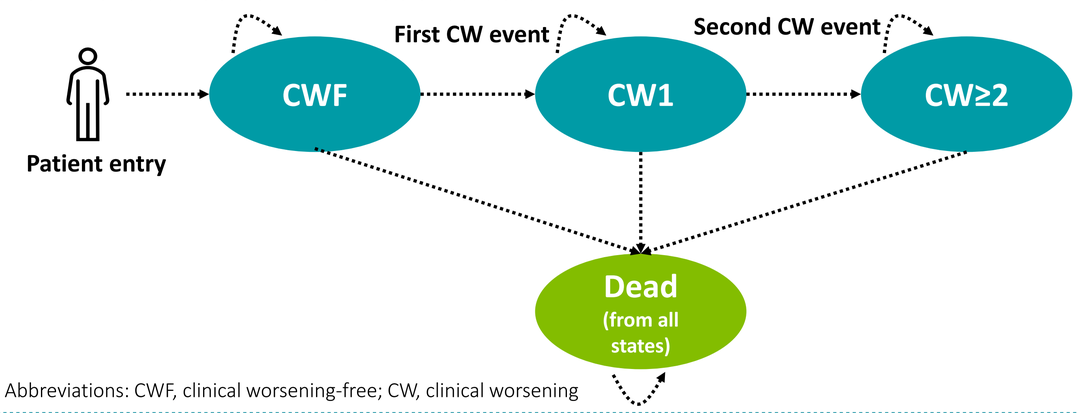
Partitioned Survival Model

A cohort-partitioned survival model (PSM) was considered most appropriate (see Figure 1). A PSM approach reflected PH-ILD disease progression and allowed for both the PH and ILD outcomes to be captured within one defined event: 'clinical worsening'. A clinical worsening event was defined as: death, decreased six-minute walking distance of ≥15% from baseline (to capture PH decline), decreased predicted forced vital capacity of ≥10% from baseline (to capture lung function decline), cardiopulmonary hospitalisation or lung-disease exacerbation. Clinical worsening reflected key INCREASE trial endpoints directly, whilst being considered clinically meaningful and prognostic by clinical experts in the advisory boards.

Time-to-event data from INCREASE were used to inform the proportion of people experiencing a clinical worsening event or dying within each weekly cycle. The model had the following four health states: clinical worsening free (CWF), one clinical worsening event (CW1), two or more clinical worsening events (CW≥2), and dead.

Whilst people with PH-ILD could experience three or more clinical worsening events, these events were not reflected in a 'three or more clinical worsening events' health state because there were insufficient data in the INCREASE 16-week and INCREASE OLE studies to perform a robust survival analysis of time to third and fourth clinical worsening events. Exploratory unpublished analysis confirmed that the St George's Research Questionnaire score, which is a measurement of health-related quality of life, between people who had experienced ≥2 events and those who experienced ≥3 events was not significantly different. Therefore, the occurrence of more than two clinical worsening events was noted to not have a meaningful impact on health-related quality of life (subject to the risk of death being equivalent for those that had two and three or more events). However, costs were applied to those people occupying the CW≥2 health state as they experienced more cardiopulmonary hospitalisations.

Figure 1. Partitioned survival model structure



Abbreviations: CWF, clinical worsening-free; CW, clinical worsening

4. CONCLUSION

A cohort PSM was considered most appropriate because it facilitated the use of a clinically meaningful and prognostic PH-ILD-specific composite measure that reflected INCREASE trial endpoints directly. No established disease severity classification systems that could appropriately reflect PH-ILD using the trial data were available. Additionally, the use of clinical worsening events enabled the use of patient-level data to inform survival curves predicting the time to clinically meaningful events and death. The advisory board attendees agreed that the chosen approach best utilised the available data. The pros and cons of this model structure are detailed in Table 1. Further research is recommended to develop, and validate, a risk-stratification system that is specific to people with PH-ILD.

Table 1. Pros and cons of using a partitioned survival model

Pros	Cons
▪ Partitioned survival models are common and applicable model structures that are frequently used when modelling a cohort of people with a progressive disease.	▪ Clinical improvement is not explicitly captured.
▪ Long-term extrapolation can be informed using parametric extrapolation of the Kaplan-Meier data of INCREASE.	▪ The heterogeneity of people with PH-ILD is not as accurately captured as it could be in a patient-level simulation.
▪ Limited data transformations are required to populate the model.	▪ Unable to distinguish any additional mortality risk between patients who experience only two worsening events and those who experience more than two.
▪ Incorporates lung function in the form of FVC%, which is expected to not be as easily done in other structures.	

Abbreviations: FVC, forced vital capacity; PH-ILD, pulmonary hypertension with interstitial lung disease

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