HTA322

Modelling antifibrotic therapies for idiopathic pulmonary fibrosis and progressive fibrosing interstitial lung disease: learnings from NICE submissions from the past decade

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Introduction

- Two antifibrotic (AF) medicines have been recommended by the National Institute for Health and Care Excellence (NICE) as treatment options for idiopathic pulmonary fibrosis (IPF) and progressive fibrosing interstitial lung disease (PF-ILD):
  - nintedanib for IPF and PF-ILD,
  - pirfenidone for IPF.
- With new interventions in development for IPF and PF-ILD, it is important to learn from previous Technology Appraisals (TAs) to identify areas for improvement.

Aim

- To review cost-effectiveness modelling methods used in NICE TAs of AF medicines in IPF and PF-ILD, and to identify the strengths and limitations of each approach.

Methods

- Publicly available final appraisal documents for IPF and PF-ILD TAs were identified from the NICE website.
- Information was extracted about the types of models used, the rationale behind the choice of model type, inputs, and extrapolation methods, as well as NICE's critiques and final recommendations.

Key themes in NICE critiques

State transitions
All TAs had the limitation that, due to the lack of suitable data, mortality risk was modelled independently of lung function decline and acute exacerbation outcomes

Extrapolation
Issues with survival curves in all TAs: log-logistic curve may underestimate survival;[3] Gompertz distribution more clinically plausible than Weibull;[2] uncertainty due to immature survival data;[5] alternative survival assumption preferred[4]

Stopping rule
Concerns in 2 TAs about stopping rules and their impact on cost-effectiveness[2,3]

Clinical assumptions
Concerns in 2 TAs about clinical assumptions, particular surrounding acute exacerbations[2,3]

Conclusions

- This review of NICE TAs highlights difficulties of economic modelling of IPF and PF-ILD.
- Key limitations include:
  - model structure (in pirfenidone TAs),
  - modelling the interdependency of mortality, disease progression, acute exacerbations and treatment discontinuation,
  - uncertainties in extrapolating survival data and treatment benefit,
  - suitability of model populations, utility values, time horizons and stopping rules.
- These areas should be considered in future NICE TAs of IPF and PF-ILD treatments.

Abbreviations

AF, antifibrotic; ERG, evidence review group; FVC%pred, forced vital capacity percentage predicted; ICER, incremental cost-effectiveness ratio; IPF, idiopathic pulmonary fibrosis; N/R, not reported; NICE, National Institute for Health and Care Excellence; OLE, open-label extension; PF-ILD, progressive fibrosing interstitial lung disease; TA, technology appraisal.

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References

1. NICE. Pirfenidone for treating idiopathic pulmonary fibrosis (TA282). 2013
2. NICE. Pirfenidone for treating idiopathic pulmonary fibrosis (TA504). 2018
3. NICE. Nintedanib for treating idiopathic pulmonary fibrosis (TA379). 2016
4. NICE. Nintedanib for treating idiopathic pulmonary fibrosis when forced vital capacity is above 80% predicted (TA864). 2023
5. NICE. Nintedanib for treating progressive fibrosing interstitial lung diseases (TA747). 2021

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Results

Overview of TAs

- Five TAs were identified: 2 for pirfenidone in IPF[1,2], 2 for nintedanib in IPF[3,4] and 1 for nintedanib in PF-ILD[5] (**Table 1**).
- With the exception of pirfenidone for IPF in the >80% forced vital capacity percentage predicted (FVC%pred) population,[2] all of the TAs resulted in a positive recommendation.
- In all TAs, lung function decline was assessed using FVC%pred.
- The 3 nintedanib TAs[3–5] utilised a 19-health-state Markov model, based on 9 categories of FVC%pred in 10% increments, the presence or absence of acute exacerbation, and death.
  - NICE preferred the 19-state model to the 3-health-state partitioned survival model used in the pirfenidone TAs.
- NICE critique fell into 8 main themes, with all TAs receiving criticism in at least one area (**Table 1**).

Table 1. Overview of NICE TAs in IPF and PPF.

🟢 Recommended/no committee concerns 🟠 Concerns expressed by committee 🔴 Committee concerns leading to negative recommendation

TA	Pirfenidone for IPF, 2013 (TA282)[1a]	Nintedanib for IPF, 2016 (TA379)[3]	Pirfenidone for IPF, 2018 (TA504)[2]	Nintedanib for PF-ILD, 2021 (TA747)[5]	Nintedanib for IPF >80% FVC%pred, 2023 (TA864)[4]
Recommended by NICE	🟢	🟢	🔴	🟢	🟢
Model overview					
Model type	Microsimulation model	19-health-state Markov model	3-health-state partitioned survival model	19-health-state Markov model	19-health-state Markov model
Population restriction	FVC%pred 50–80%	FVC%pred 50–80%	FVC%pred > 80%	FVC%pred 50–80%	FVC%pred > 80%
Modelled outcomes leading to state transition	*N/R*	• Loss of lung function (10% FVC%pred increments) • Acute exacerbation • Loss of lung function and acute exacerbation • Death: – at any point in the model (and from any health state) based on the survival analysis of the clinical trial data; or – at the point that patients reached 30% FVC%pred, assumed to be an unsustainable level of lung function	• Death (based on parametric survival curves) • Disease progression (≥ 10% absolute decline in FVC%pred within any 12-month period)	• Loss of lung function (10% FVC%pred increments) • Acute exacerbation • Loss of lung function and acute exacerbation • Death: – at any point in the model (and from any health state) based on the survival analysis of the clinical trial data; or – at the point that patients reached 30% FVC%pred, assumed to be an unsustainable level of lung function	• Loss of lung function (10% FVC%pred increments) • Acute exacerbation • Loss of lung function and acute exacerbation • Death: – at any point in the model (and from any health state) based on the survival analysis of the clinical trial data; or – at the point that patients reached 30% FVC%pred, assumed to be an unsustainable level of lung function
NICE feedback					
Model structure	*N/R*	🟢	🟠 Model only accounted for disease progression based on FVC%pred and mortality	🟢	🟢
Model population	*N/R*	🟠 Lack of patients with FVC%pred > 80%	🔴 Lack of patients with FVC%pred > 80%	🟢	🟢
State transition	*N/R*	🟠 Acute exacerbations not linked to life expectancy	🟠 Acute exacerbations not connected to disease progression and mortality	🟠 Unclear link between mortality and FVC%pred	🟠 No link between exacerbations, progression and mortality
Assumptions	*N/R*	🟠 Concern that model results were not sensitive to changes in the rate of exacerbations	🟠 Several clinically implausible assumptions, e.g. no link between time to progression, time on treatment and death	🟢	🟢
Stopping rule	*N/R*	🟠 No clinical basis for applying a stopping rule	🔴 Impact of stopping rule was uncertain	🟢	🟢
Outcome extrapolation	*N/R*	🟠 Log-logistic curve for overall survival may underestimate ICER	🔴 Disagreement over most suitable survival curve to apply	🟠 Concern over uncertainty in survival extrapolation	🟠 Conflicting approaches by company and ERG
Utility	*N/R*	🟠 Disutility for diarrhoea not included in model	🟢	🟢	🟢
Time horizon	*N/R*	🟢	🟢	🟢	🟠 A 35-year time horizon was preferred to the 50-year base case

[a]No NICE feedback available as TA282 has been replaced by TA504 following the availability of new clinical data

Extrapolation from clinical trial data

- Only 2 TAs used data extrapolated from clinical trials with a follow-up longer than 52 weeks (**Figure 1**).
  - The only TA to receive positive feedback on its extrapolation approach used data from an open-label extension (OLE; TA864).[4]

Exploratory analyses

- Exploratory analysis conducted by the evidence research group (ERG) and subsequent changes to the model by the company can also highlight issues in economic models.
- Additional analyses addressed multiple aspects of the models (**Figure 2**).
  - In particular, the use of different survival curves for extrapolation of trial data was explored in all 4 TAs.

Figure 1. Follow-up length in clinical trials used in TAs.

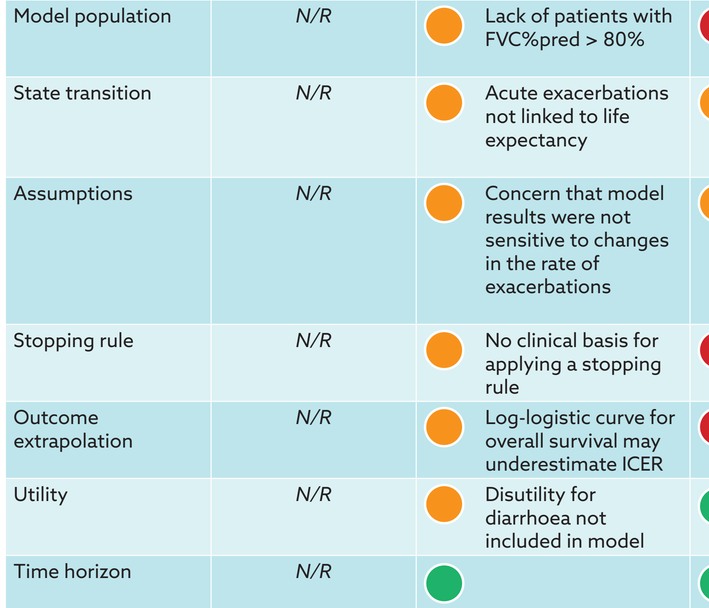
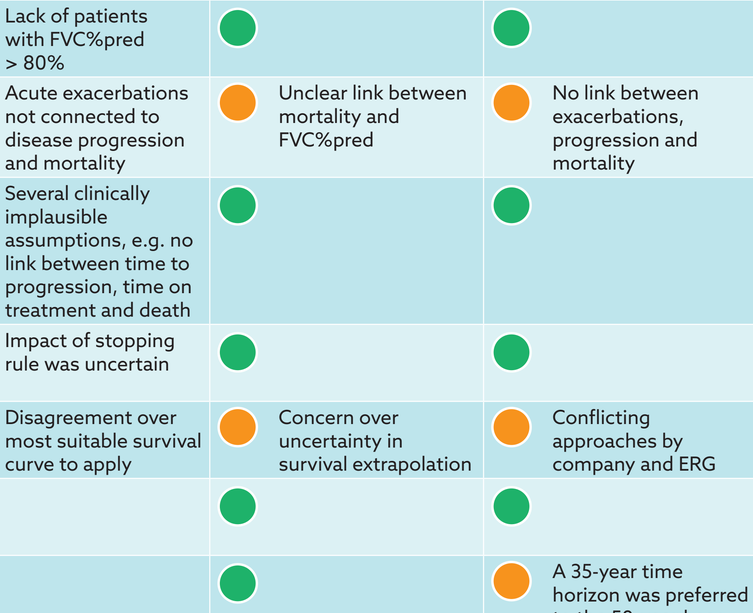


Figure 2. Additional analysis following ERG review.



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