Cost-effectiveness Model Conceptualisation in Fibrodysplasia Ossificans Progressiva

EE243

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Background

- Fibrodysplasia ossificans progressiva (FOP) is an ultra-rare genetic disorder of progressive irreversible heterotopic ossification (HO) in soft and connective tissues.[1] HO growth is often preceded by severely painful and physically debilitating swellings termed 'flare-ups'.
- Current treatment options for people with FOP are limited; there is no definitive standard of care (SoC).[2]
- Studies of experimental therapies have focused on HO volume to quantify therapeutic benefit. Palovarotene has been reported to reduce the development of new HO in people with FOP (MOVE trial; NCT03312634) versus a natural history study (NHS; NCT02322255).
- HO needs to be linked to outcomes such as mortality, morbidity, and quality of life (QoL) for a cost-effectiveness model (CEM).

Objective

To conceptualise the first long-term CEM comparing palovarotene to SoC in people with FOP.

Methods

- Model conceptualisation relied on FOP literature and MOVE/NHS data, focusing on links between HO and outcomes such as QoL and costs.
- A burden of illness (BoI) study (NCT04665323) was available, which collected data on the economic impact of FOP on patients and their family members, alongside measures of joint impairment, body regions affected by HO, and QoL.[3]
- The model concept was validated in individual structured interviews with clinical (N=2) and health economic experts (N=3).

Results

- Multiple concepts to describe the underlying FOP disease process were explored. **Figure 1** shows the main concepts and interactions within FOP and the potential impact of palovarotene on the disease.
- Flare-ups as drivers of disease progression were ruled out as many studies reported disease progression without flare-up symptoms.[4] However, flare-ups still need incorporating into the model as they influence frequency of treatment. Previously conducted studies in FOP observed that the average number of flare-ups in a given year reduce with age.[5]
- Total body HO is a common clinical trial endpoint because it is measurable over the relatively short-term course of a clinical study and may be sufficiently sensitive to document estimated disease progression and treatment effect.[5]
- Therefore, the most supported structure is a Markov model consisting of states with increasing whole body HO volume.
- The model should have the ability to run for each year of age of starting treatment to capture age-appropriate numbers of flare-ups, HO growth, increases in drug usage over time (both for palovarotene and SoC) and increased mortality with age.
- Existing literature indicates that the transition to higher volume HO states slows down after 25 years of age, and can be used to calculate progression through HO states.
- No studies directly linking HO volume to QoL and costs exist. However, increase in HO volume is associated with increases in mobility restrictions as measured by cumulative analogue joint involvement scale (CAJIS) scores, which can be linked to QoL and costs (**Figure 2**).

Figure 2. Link between clinical and economic outcomes

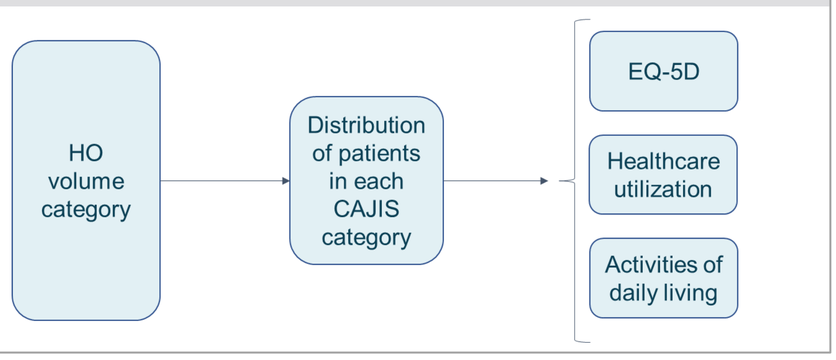
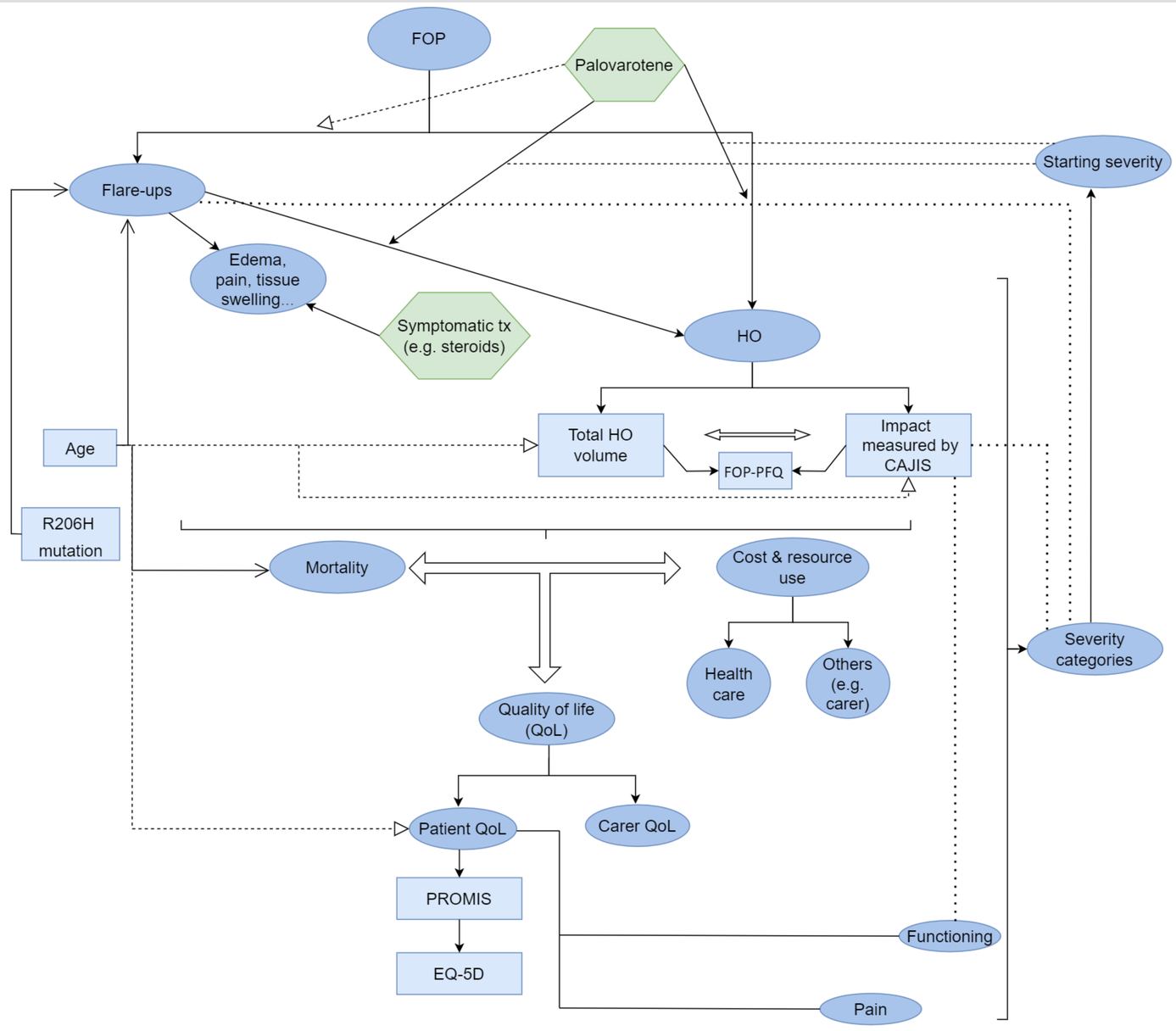


Figure 1. Influence diagram of FOP



Legend: Green hexagons: treatments to be considered in the economic evaluation; Blue ovals: concepts to be captured in the evaluation; Light blue rectangles: measurements of above concepts; Solid arrows: direct evidence available on the relationship; Dotted arrows: correlation observed, indicating potential relationship; Wide arrows: hypothesised relationship to be calculated by model

- Explicit quantification of the CAJIS-HO relationship was avoided as they are not perfectly correlated, with each HO state associated with a distribution of patients between CAJIS categories as observed in the NHS, and higher HO categories having more patients with higher CAJIS scores.[5]
- For QoL, the MOVE trial collected PROMIS scores, which could be mapped to EQ-5D-3L.[6] Alternatively, the BoI survey collected EQ-5D-5L directly. Both sources show a profound impact of worsening health state represented by worsening CAJIS scores on QoL.
  - –Carer utilities are also available from the BoI survey, and could be an important element to include in a disease where full time care may be required for a person with severely affected joints.
- For costs, the BoI survey found that the number of living adaptations used by patients generally increased with CAJIS level, alongside an increase in healthcare utilisation and financial impact of FOP on patients and their families. Thus, it is anticipated that over time, higher volumes of HO will also be associated with higher costs.
- Serious treatment-emergent adverse events associated with treatment would be included as reported in MOVE.
- A study published on survival observed that people with FOP live to a median age of 56 years, with excess mortality becoming particularly apparent in patients from the age of 30.[7] The leading cause of death was thoracic insufficiency syndrome due to ankylosis of the costovertebral joints.
  - –The MOVE trial was not long enough to capture the impact of palovarotene on mortality.
  - –There may be potential for palovarotene to improve survival outlook through delaying accumulation of HO, and thus delaying conditions such as thoracic insufficiency syndrome.
- **Limitation**: Location of HO accumulation is important, however, due to lack of data, it was not possible to model HO in individual joints.

CONCLUSIONS

- **By preventing new HO, palovarotene has the potential to positively impact patient outcomes in FOP. Correlation between HO volume and CAJIS score has been demonstrated, although the relationship is far from perfect and depends on the age of the patient. Therefore, the proposed model structure avoided direct linkages and forcing change in one parameter (e.g. CAJIS) due to a change in another (e.g. HO), relying on shifts in distributions between categories instead.**
- **Identification of a study quantifying the impact of CAJIS on outcomes of importance for the economic assessment allowed the linking of HO volume as measured in the trials to long-term outcomes for a CEM.**
- **Over and above the usual sensitivity analyses, extensive scenario analyses will be required to test the impact of structural assumptions in the model as well as around categorisations of measures used.**
- **Model conceptualisation in ultra-rare diseases with limited data relies heavily on expert validation to identify main disease drivers (HO and CAJIS in this case) and aspects influencing the disease and treatment patterns (such as the impact of age on HO and flare-ups).**

Abbreviations BoI: burden of illness; CAJIS: cumulative analogue joint involvement scale; CEM: cost-effectiveness model; EQ-5D: EuroQol-5 Dimension; FOP: fibrodysplasia ossificans progressiva; FOP-PFQ: FOP Physical Function Questionnaire; HO: heterotopic ossification; NHS: natural history study; PROMIS: Patient-Reported Outcomes Measurement Information System; QoL: quality of life; SoC: standard of care.

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References available with poster download

? For further information, please send your question(s) to **Elaine.Boing@ipsen.com**

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