Structuring value elements for cost-effectiveness modelling: the STEPPS framework applied to fazirsiran in alpha-1 antitrypsin deficiency-associated liver disease

Poster MSR152

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Introduction

- Health technology assessment (HTA) increasingly seeks patient input – the EU HTA Regulation makes provision for patient engagement as part of its Joint Clinical Assessments[1] – but informing economic model development is the least developed contribution of qualitative evidence to HTA.[2]
- Value frameworks have proposed additional elements beyond the standard cost-effectiveness approach. However, these frameworks do not provide a structure for deciding which to include in a model, which to address outside the model and which fall outside conventional modelling altogether.[3]
- This challenge is critical in relation to rare genetic diseases, where diagnostic burden, uncertainty, stigma, caregiver impacts and the value of hope may be important but are difficult to represent consistently.
- Fazirsiran is an investigational siRNA therapy for alpha-1 antitrypsin deficiency-associated liver disease (AATD-LD), currently in phase 3 clinical trial. In the protease inhibitor (Pi)*ZZ genotype, misfolded alpha-1 antitrypsin protein accumulates in hepatocytes and drives liver disease progression through fibrosis to cirrhosis, decompensation, hepatocellular carcinoma (HCC) and ultimately a need for transplantation.
  - Early disease is largely asymptomatic, and outcomes are poor in the later stages.
- No disease-modifying treatment exists for AATD-LD; management consists of monitoring, risk-factor reduction and transplantation in advanced disease.

Aims

- To propose a structure for organizing value elements that corresponds directly to the specification of a health economic model, and to apply it to fazirsiran in AATD-LD.
- Three connected contributions are proposed: the STEPPS framework; a three-state conceptual model of silent, known and treatable disease; and an account of the value elements that sit outside the model.

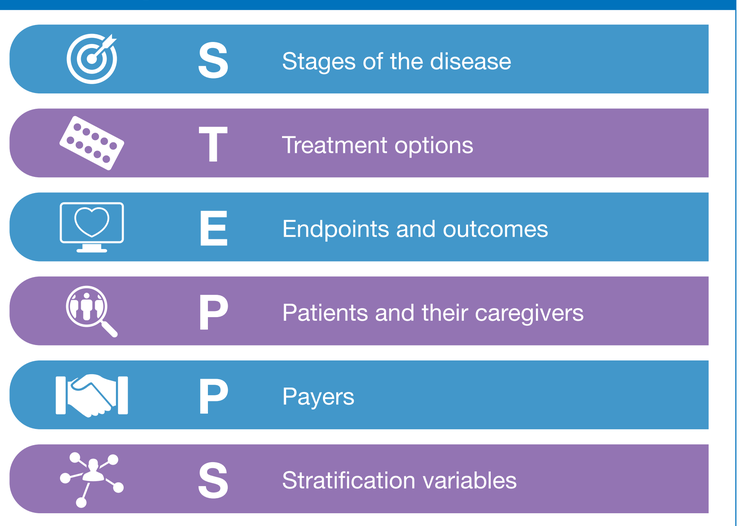
Methods

- The starting point was an existing inventory of 103 value elements across 24 value components and four value domains, developed in earlier work with clinicians, payers and patient representatives, and taken as given in this study. The sponsor had prioritized these to approximately 50 elements, organized with reference to the target product profile and classified as core, exploratory or supportive.
- The STEPPS framework was devised as an alternative organization of these value elements (**Figure 1**).
- Eight internal stakeholders were interviewed individually about the value elements and their fit to the framework: the five-member project team, including the sponsor's patient advocacy lead, and three colleagues with experience of developing value propositions for new medicines.
- The interviews informed the mapping of the prioritized value elements to the framework (**Table 1**).
- A conceptual model was derived to cover as many value elements as possible (**Figure 2**), and the value elements the model does not capture were identified.
- A patient advisory group was consulted separately on the design of a further stage of qualitative research with patients.

Results

Figure 1. The STEPPS framework

Each STEPPS dimension corresponds to a decision in specifying the model, so organizing value and specifying model architecture become a single exercise.



- Unlike conventional value-element taxonomies, each dimension in STEPPS relates to a specific part of a decision the modeller has to frame.
- The perspective of the analysis – health service or societal – adds depth to the patient and payer dimensions in particular.

Table 1. Model elements and mapped value elements by STEPPS dimension

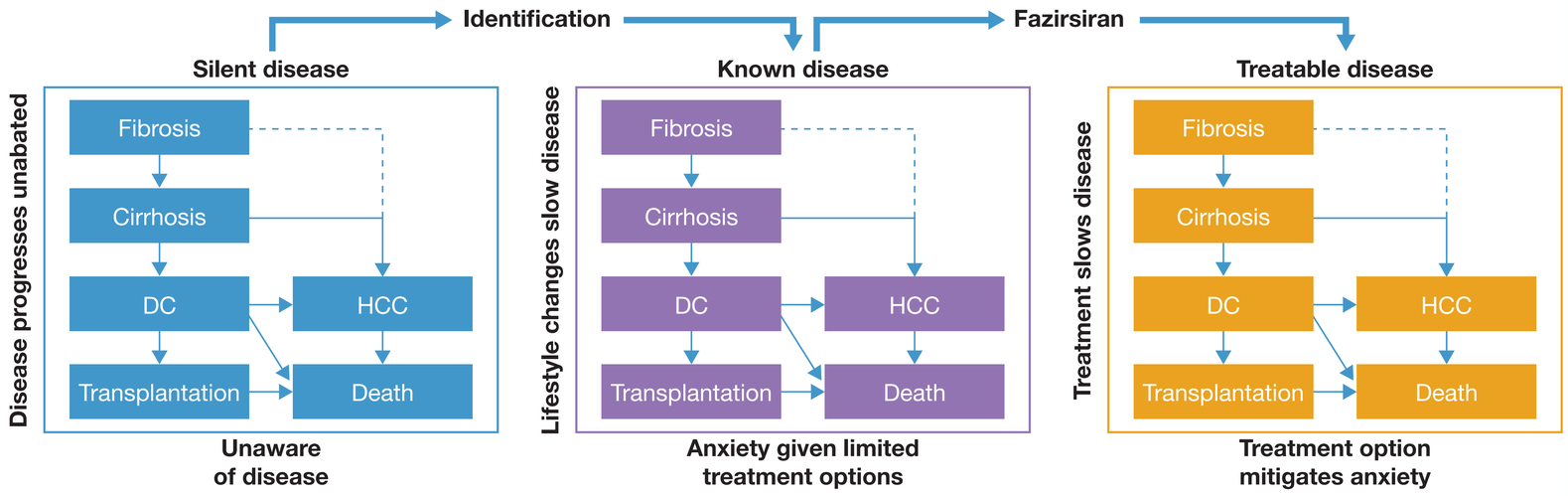
The prioritized value elements map onto the four central STEPPS dimensions; the outer two are structural.

Dimension	Model element	Value elements mapped
S Stages of disease	Fibrosis, cirrhosis, DC, HCC, transplantation	Structural
T Treatment options	Fazirsiran, management, identification strategies (early diagnosis, case finding)	Halting or regressing liver fibrosis, preventing or delaying end-stage liver disease and the need for transplantation; starting treatment early, improving long-term outcomes against lifestyle management or transplantation; AATD-LD-specific diagnosis and treatment recommendations
E Endpoints and outcomes	Time to cirrhosis, time to transplantation, rates of HCC, death	Better understanding of the natural history of the disease, linking short- and long-term outcomes
P Patients and their caregivers	Quality of life, out-of-pocket costs, caregiver burden, productivity losses	Patient productivity, treatment burden, caregiver and family burden, patient out-of-pocket costs
P Payers/HTA	QALYs, healthcare costs	Health system impact across diagnosis, treatment and transplantation; quality of life of patients; length of life of patients; provider impact
S Stratification variables	Comorbid lung disease	Structural

- Stages of disease and stratification variables fix the states that the model moves between and the subgroups it distinguishes, providing the skeleton against which value is realized.

Figure 2. Conceptual model of AATD-LD including identification

Diagnosing a debilitating genetic condition for which no effective treatment exists is itself value-relevant and gives an effective treatment dual value – improving prognosis and mitigating the anxiety induced by diagnosis.



Dashed arrow indicates the low-rate transition in patients with advanced fibrosis (F3).

- The conceptual model places a common progression chain – fibrosis → cirrhosis → decompensated cirrhosis and/or HCC → transplantation → death – within three states of the disease: silent, known and treatable.
- In silent disease, the condition progresses unabated and the patient is unaware of it. Identification moves the patient to known disease, where lifestyle changes may slow progression, but the diagnosis itself plausibly reduces quality of life. An effective treatment moves the patient to treatable disease, where progression is slowed and the anxiety induced by the diagnosis is mitigated.
- Fibrosis is represented as a single state, because the individual stages of fibrosis indicate time to the longer-term sequelae, but have little impact on the patient before symptoms emerge at cirrhosis.
- HCC is retained in the model, although data on HCC risk in AATD-LD are limited and one transplantation-referral cohort found lower rates than in cirrhosis of other causes.[4]

Table 2. Value elements outside the model and how they are handled

Value elements outside conventional modelling scope are best handled as deliberative decision factors or through targeted extension of the framework.
- **Of these, stigma and the value of hope appear particularly material in AATD-LD.**

Category	Value element	How it is handled
Deliberative decision factor	Scientific spillovers	Accrued to every technology brought to market, and to those that fail, so there is no differentiation between technologies
Deliberative decision factor	Severity and rarity	Considered to be contextual factors or modifiers to the cost-per-QALY threshold
Targeted framework extension	Transplantation-community benefit	Organs not needed by treated patients go to other recipients on the waiting list; their health gain can be valued if the cost associated with the transplant they receive is counted and not booked as a saving
Targeted framework extension, with patients	Stigma	Liver disease is commonly associated with alcohol use and obesity, so identifying AATD as the cause could reduce stigma, including for people who progress to symptomatic disease. How the hereditary nature of AATD affects stigma is a question for qualitative research with patients
Targeted framework extension, with patients	Value of hope	Not traditionally captured, but could be, subject to the design of appropriate research with patients

Limitations

- The framework and the conceptual model are derived from a single indication and a single value-element inventory and have not been tested in other disease areas.
- The value elements were prioritized and mapped without direct patient input.
- Stigma and the value of hope are identified as material to value in AATD-LD, but are not yet represented; how they should be quantified remains open.

Conclusions

Key takeaways

- STEPPS separates the value elements that can be modelled from those better addressed through deliberation or through targeted extension of the framework, and directs methodological attention to those that matter most.
- The three-state conceptual model makes the value of diagnosis explicit and gives an effective treatment a dual role: prognostic and psychological.
- Together they provide a transparent basis for incorporating patient experience into value assessment.

Future directions

- Stigma and the value of hope are the priority value elements to take to patients. Understanding the nature and extent of these elements, and how they might be represented in an economic analysis, requires formal qualitative research rather than consultation.
- Qualitative evidence is rarely used to inform model structure: one of 231 submissions to the UK NICE and CADTH did so.[5]
- The next stage is qualitative research with direct patient involvement, under its own protocol and ethical approval, to elicit the value elements prioritized by patients and co-produce the model on that basis.

Abbreviations

AATD-LD, alpha-1 antitrypsin deficiency-associated liver disease; CADTH, Canadian Agency for Drugs and Technologies in Health; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; Pi, protease inhibitor; QALY, quality-adjusted life-year; STEPPS, stages of disease, treatment options, endpoints and outcomes, patients and their caregivers, payers, and stratification variables.

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