Clinical development of new technologies for non-alcoholic steatohepatitis: NICE perspective
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Balancing Clinical and Cost Effectiveness

*A game of two halves?*

How cheap does this technology need to be to make it cost effective?

How clinically effective does this technology have to be to make it worth paying that much for?

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One in, one out?
Assessing Cost Effectiveness

\[ ICER = \frac{\text{Incremental costs}}{\text{Incremental effectiveness}} = \frac{\text{Cost}_A - \text{Cost}_B}{QALY_A - QALY_B} \]

= Cost per 1 QALY

QALY: Quality Adjusted Life Years
Assessing Cost Effectiveness

Probability of rejection vs. Cost per QALY (£000)

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NICE Committee decision making

- Clinical effectiveness
- Other health benefits
- Innovation
- Equality legislation
- Social Value Judgements
- Extent of uncertainty
- Cost-effectiveness

Recommendations
Non-alcoholic steatohepatitis (NASH)

• NASH is a non-alcoholic fatty liver disease characterised by hepatocellular injury, inflammation, and progressive fibrosis.

• NASH may lead to cirrhosis, hepatic decompensation, hepatocellular carcinoma and death.

• NHS practice reflected in NICE guidance published in NICE guideline 49 (6 July 2016).
Consider bariatric surgery AND all appropriate non-surgical measures have been tried but the person has not achieved or maintained clinically beneficial weight loss (NICE CG 189).

Risk factor for type 2 diabetes [atrial fibrillation, myocardial infarction, ischaemic stroke and death from cardiovascular causes], hypertension and chronic kidney disease

No routine screening NASH should be suspected in higher-risk groups: type 2 diabetes, metabolic synd. Diagnosed on the basis of an ultrasound

Risk factors and identification

Testing and diagnosis of children and young people

Non-alcoholic fatty liver disease
Advanced liver fibrosis in adults (NG49)

Person aged 18 or over with confirmed non-alcoholic fatty liver disease

Testing, diagnosis and referral of advanced liver fibrosis

Pioglitazone or vitamin E

Reviewing treatment

Monitoring for cirrhosis

Biomarkers (ELF test) are used to diagnose presence of fibrosis

Diagnose advanced liver fibrosis if:
- ELF score of 10.51 or above
- and NAFLD

(if advanced liver fibrosis)

Consider using the ELF test to assess whether pharmacological therapy is effective

Reassessment for advanced liver fibrosis every 3 years
Advanced liver fibrosis in young children and young people (NG49)

- Biomarkers (ELF test) are used to diagnose presence of fibrosis
- Diagnose advanced liver fibrosis if:
  - ELF score of 10.51 or above
  - and NAFLD
- Consider using the ELF test to assess whether pharmacological therapy is effective
- Reassessment for advanced liver fibrosis every 2 years

Person over 1 and under 18 with confirmed non-alcoholic fatty liver disease

Testing and diagnosis of advanced liver fibrosis

Vitamin E (if advanced liver fibrosis)

Reviewing treatment

Monitoring for cirrhosis
## Elements of an appraisal: scope

<table>
<thead>
<tr>
<th>Item of the appraisal</th>
<th>Content of the scope</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>When the technology is a medicine, the marketing authorisation will generally specify the therapeutic indications.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>The scope includes information about the marketing authorisation (or CE mark for medical devices) of the technology, and the stage of regulatory approval for technologies not yet licensed.</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Established NHS practice.</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>The clinical outcome measures usually quantify an impact on <strong>survival</strong> or <strong>health-related quality of life</strong> that translates into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness.</td>
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</tbody>
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Population

Main advice on patients selected in trials:
- NASH diagnosis is not made on the basis of a liver biopsy in the NHS.
- Biomarkers (ELF test) can be used to diagnose presence of fibrosis.
- If liver biopsies are performed, possible to correlate the findings with biomarkers information.
Population

- Heterogeneous population with different degrees of severity of the disease: liver fibrosis (stages 1 – 3).
- Treatment could be relevant in patients who have not responded to lifestyle modification advice:
  - Standardisation of eligibility criteria,
  - Consider including patients with compensated liver cirrhosis.
Comparators

NHS current practice:
• Pioglitazone and vitamin E in patients with advanced disease (stages 2 and 3).

NHS current practice may change if a new medicine is authorised and becomes reference treatment in the NHS.
• Consider indirect treatment comparisons.
Outcomes

- NICE uses outcomes of relevance to patients and their carers:
  - Survival
  - Improved quality of life (EQ-5D)
- NICE generally supported endpoints aimed at assessing evolution of fibrosis.
- Fibrosis assessed with ELF test are associated with disease progression (Sanyal et al. 2017).
Outcomes

- Other relevant endpoints for NASH:
  - Hepatic conditions:
    - Progression to cirrhosis,
    - Liver transplant,
    - Hepatocellular carcinoma,
    - Death.
  - Extra-hepatic conditions:
    - Type 2 diabetes, hypertension and chronic kidney disease,
    - Cardiovascular diseases and death.
Outcomes

• Important to determine the relationship between improvement and resolution of NASH with changes in fibrosis and changes in quality of life (HRQL), survival and resource use.

• Long term follow-up of patients is important (generally beyond the duration of clinical trials).
Quality of life

- HRQL of patients with NASH not adversely affected even in advanced disease: mostly fatigue.
- Difficult to disentangle decrement in HRQL linked to NASH or to co-morbidities (type 2 diabetes).
- Regular administration of HRQL questionnaires (e.g. every 3 months).
Economic Modelling: principles

Model should reflect the natural evolution of the disease.

Health benefits (QALY gain) and resources measured and modelled for each state.

Derive cost/QALY
Economic Modelling

General comments:
• NICE does not have any preferred model.
• Health states should represent homogeneous and clinically distinct groups.
• Robustness and plausibility of assumptions.

Specific modelling issues:
• Discrete event simulation may better capture the intrinsic variability within population of diseases such as NASH.
Economic Modelling

• Liver transplant stage:
  • Only patients with (advanced) liver cirrhosis or hepatocellular carcinoma would be eligible for a liver transplant in the NHS.

• Post liver transplant stage.

• Important to include a “Death” stage.

• Consider stopping rules based on treatment response (e.g. ELF test).
Remember to …

• Incorporate HTA requirements in addition to regulatory requirements.
• Develop a sound value proposition of the new technology (delay or reversal of fibrosis, prevent liver transplant or improve survival).
• Plan economic evaluation with clinical development.
• Engage with HTA agencies and regulators thorough the development cycle, do not hesitate to seek HTA scientific advice.
Useful links

Non-alcoholic fatty liver disease overview
https://pathways.nice.org.uk/pathways/non-alcoholic-fatty-liver-disease

Non-alcoholic fatty liver disease (NAFLD): assessment and management. NICE guideline [NG49]
https://www.nice.org.uk/guidance/ng49

Office for Market Access
https://www.nice.org.uk/about/what-we-do/office-for-market-access

Technology appraisal guidance
https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technology-appraisal-guidance
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