Liothyronine for hypothyroidism: a candidate for disinvestment or in need of further research? A value of information analysis

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ABSTRACT

Objective Medicines with limited evidence of effectiveness are prime candidates for disinvestment. However, investment in further research may be preferable to deimplementation, given that the absence of evidence is not evidence of absence, and research can inform formulary decisions. A case in point is liothyronine, which is sometimes prescribed to levothyroxine-treated patients who continue to experience hypothyroid symptoms. It is a putative low value medicine, associated with uncertainties in both clinical and cost-effectiveness. The aim was to assess the cost-effectiveness of liothyronine in this context, and estimate the value of conducting further research.

Design Cost utility and value of information analyses.

Setting Primary care within the National Health Service in the UK.

Participants Fifty-four levothyroxine-treated patients with persistent symptoms of hypothyroidism.

Interventions Liothyronine plus levothyroxine versus levothyroxine alone.

Primary and secondary outcome measures Incremental cost per quality-adjusted life year (QALY) gained, and the expected monetary value of sample information.

Results 20/54 (37%) of patients who responded to the survey reported severe problems in carrying out usual activities of everyday living and 12/54 (22%) reported severe anxiety or depression symptoms. Mean (SD) utility was 0.53 (0.23). The differences in expected total, 10-year costs and QALYs between a treatment strategy of liothyronine/levothyroxine combination therapy, and levothyroxine alone, was £12,053 and 1.014, respectively. The incremental cost-effectiveness ratio of £11,881 per QALY gained was sensitive to the price of liothyronine. The probability of liothyronine/levothyroxine combination therapy being cost effective at a threshold of £20,000 per QALY was 0.56. The value of reducing uncertainty in the efficacy of treatment was £3,64 m per year in the UK.

Conclusions A definitive clinical trial to confirm clinical effectiveness may be preferable to immediate disinvestment, and would be justified given the value of the information gained far exceeds the cost.

INTRODUCTION

Disinvestment from healthcare interventions and practices that are considered to offer no or low value is a strategy being used increasingly by healthcare systems around the world in response to unprecedented pressures on budgets. Within the National Health Service (NHS) in the UK, there has been a specific focus on older medicines—such as those which gained marketing authorisation in an era when the evidential standards were lower; or which have been largely supplanted by newer, more effective or safer medicines; or whose use has become marginalised resulting in variation in care, or monopoly of supply leading to price inflation. Health technology reassessment (HTR) describes the process of judging the value of such medicines, and determining whether they warrant continued use, more expanded use or disinvestment (deimplementation). HTR methods may also allow for an assessment of the value of conducting further research to reduce the...
uncertainty surrounding a medicine’s clinical and cost-effectiveness. In such cases, continuing the status quo may be reasonably justified while new evidence accrues.

Liothyronine is an epitome, first licensed for the management of hypothyroidism in 1956, but replaced by levothyroxine which offers more favourable dosing and stable serum thyroid hormone concentrations. However, 5%–10% of levothyroxine-treated patients continue to experience profound and sometimes disabling symptoms, such as fatigue, depression and impaired cognition, despite achieving thyroid hormone concentrations within reference range. A proportion of these patients are prescribed liothyronine, usually in addition to levothyroxine.

Clinical guidelines advise against the routine prescribing of liothyronine. The European Thyroid Association recommends that liothyronine/levothyroxine combination therapy might be considered as an experimental approach in hypothyroidism for patients who are adherent to levothyroxine, yet experience persistent symptoms despite serum thyroid stimulating hormone (TSH) values within the reference range. The American Thyroid Association notes that there is currently insufficient evidence to support the routine use of combination therapy outside a formal clinical or N-of-1 trial; and largely based on these guidelines, the British Thyroid Association recommends that liothyronine/levothyroxine combination therapy may only be considered by endocrinologists for patients who have unambiguously not benefited from levothyroxine.

The use of liothyronine in the UK has been further discouraged because of significant price inflation due to monopoly status of the generic supplier since it was de-branded in 2007. The current price of 28 tablets of 20 µg liothyronine is £165.18, compared with £26.15 in 2010. This resulted in the NHS listing liothyronine as a medicine that should not be prescribed routinely in primary care.

Clinical guidelines acknowledge the limited evidence-base for liothyronine. While 13 trials of combination versus levothyroxine monotherapy have been reported, the majority are underpowered, some are unlikely to have tested the correct dose of liothyronine, and none restricted recruitment to patients who did not feel significantly better on levothyroxine alone. This latter point could explain why liothyronine/levothyroxine combination therapy has not demonstrated superiority, even in the larger trials. Walsh et al. found no statistically significant difference in patient well-being, quality of life or cognitive function. Appelholz et al. reported that patients preferred combination therapy but there were no differences in clinical endpoints; and Saravanan et al. did not find a significant difference in General Health Questionnaire-12 scores.

The National Institute for Health and Care Excellence (NICE), in its clinical guideline on thyroid disease, recommended that further research should be undertaken on the clinical-effectiveness and cost-effectiveness of liothyronine/levothyroxine combination therapy compared with levothyroxine for people with hypothyroidism whose symptoms have not responded sufficiently to levothyroxine alone. However, a formal analysis of its clinical and cost-effectiveness was not undertaken.

The aim of the present study was to undertake an HTR focusing on the cost-effectiveness of liothyronine in this context and adopting the perspective of the NHS in the UK, to assess the value of conducting further research to ascertain the clinical effectiveness of liothyronine as a treatment for people with treatment-unresponsive hypothyroidism.

METHODS
Overview
An economic model was developed to estimate the cost-effectiveness (incremental cost per quality-adjusted life year, QALY gained) of liothyronine/levothyroxine combination therapy. Health utilities were obtained from a survey of hypothyroid patients. The likelihood of the addition of liothyronine in returning patients to age-matched population health was based on the survey of endocrinologists and general practitioners (GPs), who also provided estimates of patients’ use of healthcare resources. The perspective of the NHS was adopted, with a 10-year time horizon of analysis. The economic analysis is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards statement.

Population
The model represented a population of patients diagnosed with primary hypothyroidism who remain actively symptomatic with levothyroxine despite being adherent with free T4 within normal ranges (9–25 pmol/L) and euthyroid serum TSH concentrations (0.4–4.0 mU/L). The cohort represented adults aged 50 years on entry to the model, consistent with the mean age of diagnosis of hypothyroidism. The simulated cohort was followed for 10 years, a period considered to be sufficient to capture differences in costs and outcomes between the treatment strategies.

Intervention
In the model, patients could continue levothyroxine alone, representing usual care in the majority of cases, or alternatively trial a 3-month period of liothyronine in combination with levothyroxine. Following the 3-month period, responders may continue liothyronine/levothyroxine combination therapy for the remainder of the 10-year time horizon of analysis. Non-responders discontinue liothyronine and revert to levothyroxine monotherapy. The base-case analysis assumed an average dose ratio of 1.3, corresponding to a daily dose of 17 µg of liothyronine and 50 µg of levothyroxine. The dose of levothyroxine monotherapy was assumed to be 100 µg/day.
Model structure
A decision tree was constructed (online supplemental appendix figure S1), in which 10-year expected costs and QALYs were estimated, and discounted at 3.5% per annum.29

Health utilities
Literature searches did not identify any relevant health utility data.20 Self-selecting people who reported to be clinically unresponsive to levothyroxine alone despite being biochemically euthyroid were recruited to a survey that was advertisement via social media, and hosted on the website of the charity Thyroid UK. Consent was obtained within the online form, following a full explanation of the purpose and nature of the survey. Those who consented were invited to complete the online survey, which included the validated, multi-attribute health utility instrument, the EuroQol EQ-5D-5L questionnaire and accompanying EQ-VAS (visual analogue scale).21 The EQ-5D-5L questionnaire asks about five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. EQ-5D-5L profiles were converted to EQ-5D-5L index values based on the EQ-5D-5L/3L cross walk value set for the UK22 in line with current best practice.23 Utility scores of 0 and 1 correspond to death and full health, respectively.

In the model, patients who responded to liothyronine/levothyroxine combination therapy were assumed to adopt age-matched population norm EQ-5D-3L utility values.24 Patients entering the model, and remaining symptomatic to either levothyroxine monotherapy or in addition to liothyronine were assumed to experience the health utilities of the sample surveyed.

Mortality
The model applied standard mortality rates of the UK general population for 2016/2018,25 on the basis of no evidence of mortality differences in treated hypothyroid patients.26

Resource use
There was no published data on NHS healthcare resource use and costs for the indication under consideration. Therefore, a survey of endocrinologists and GPs across Wales and the North West of England was conducted to estimate resource use in patients who were in each of the three branches of the decision analytic model. Clinicians recruited by one of the authors (AH) or the All Wales Therapeutic and Toxicology Centre were contacted and invited to complete the questionnaire. Categories of resource use included contacts with healthcare professionals (GP surgery visits, endocrinologist outpatient appointments and phlebotomists), thyroid function and associated tests (including TSH, free T4, free T3, TSH receptor antibodies TRAb and thyroid peroxidase TPO antibody testing), and safety monitoring tests (including, ECG, echocardiogram, bone densitometry).

Unit costs
The unit costs of NHS care were derived from the NICE guideline16 and from standard sources,27 based on a 2018/2019 cost year (table 1), and reported in British pounds (£).

Clinical effectiveness
Published clinical trials and systematic reviews9 16 were assessed for relevant data on the clinical effectiveness of liothyronine/levothyroxine combination therapy. None of the trials restricted their inclusion criteria to (or performed a subgroup analysis of) the population of interest and were therefore not considered relevant to inform the decision problem. A survey was therefore undertaken, to elicit plausible estimates of treatment effect from endocrinologists and GPs experienced in prescribing liothyronine.28 They were asked what proportion of patients would be expected to improve following a 3-month trial period with liothyronine/levothyroxine combination therapy. The mean of all responses was used in the base-case analysis.

Analysis
In the base-case deterministic analysis, the expected costs and QALYs were compared incrementally to estimate the incremental cost-effectiveness ratio (ICER):

\[
\text{ICER} = \frac{\text{COST}_{\text{LEVOthyroxine}} - \text{COST}_{\text{liothyronine+levothyroxine}}}{\text{QALY}_{\text{liothyronine+levothyroxine}} - \text{QALY}_{\text{LEVOTHYROXINE}}}
\]

Uncertainty analyses
A series of one-way sensitivity analyses was performed to assess the impact on the ICER of varying: the probability of liothyronine/levothyroxine combination therapy; the time horizon of analysis; discount rates (0% and 6% per annum); the cost of liothyronine; the age of patients in the cohort; and of using EQ-VAS for utility in patients who remain symptomatic.

The extent to which the ICER changed when simultaneously varying the probability of patients responding to liothyronine/levothyroxine combination therapy, and the annual cost of liothyronine, was assessed in a two-way sensitivity analysis.

A probabilistic sensitivity analysis (PSA) was conducted for the simultaneous consideration of uncertainty in all model parameters (costs, QALYs and probability of treatment response). Uncertainties in these parameters were represented by relevant distributions and using Monte Carlo simulation with 10 000 replications to establish the probability of liothyronine/levothyroxine combination therapy being cost-effective for different threshold values of willingness to pay. Cost-effectiveness acceptability curves29 were constructed to represent this relationship and to facilitate comparison with the NICE thresholds of £20 000–£30 000 per QALY operating in the UK.29
For the PSA, the number of prescriptions and costs of medicines were assumed to be fixed. For other items of resource use, annual quantities (and the initial 3 months in the case of liothyronine) were sampled from gamma distributions with means and SD based on responses to the survey. These were each multiplied by their respective unit costs. Utilities representing the general population norms were sampled from beta distributions with means and SD as reported by Kind et al.24 EQ-5D utility values (U) from the sample of hypothyroid patients were transformed (1−U), and the parameters of a gamma distribution (α, β) were estimated via maximum likelihood for (1−U)~gamma (α, β). The probability of responding to liothyronine/levothyroxine combination therapy was sampled from a beta distribution fitted to the reported range of expert opinions.

Value of information analysis
In order to determine the value of conducting additional research to reduce uncertainties in the model, a value of information analysis was conducted using the Sheffield Accelerated Value of Information (SAVI).30 Value of information analysis aids understanding of the acceptability of the existing uncertainty compared with the investment needed to obtain the necessary evidence that would reduce that uncertainty, enabling a decision to be made with existing information or whether to invest in further research to inform decisions with more evidence. We calculated the Expected Value of Perfect Information (EVPI) per person and overall, the Expected Value of Partially Perfect Information (EVPPI) to identify those parameters that contribute most to the decision uncertainty and the Expected Value of Sample Information (EVSI) to measure the potential value of a future clinical trial.

Software
The cost-effectiveness analysis and sensitivity analyses were performed in Microsoft Excel 2016. Macros used to run simulations for the PSA were written in Visual Basic for Applications. The value of information analysis was conducted using SAVI.30

Model validation
Validation checks were made in accordance with the AdViSHE tool.31 Development and validation of the model structure was in consultation with endocrinologists, and based on best practice and clinical guidelines for trialling liothyronine prior to its long-term prescribing. The face validity of data used as inputs to the model was both a function of findings from systematic review of the clinical literature, and the opinions of clinicians (endocrinologists and GPs) with expertise (internationally renowned in two cases) and/or experience in

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**Table 1** Resource use and unit costs per intervention group, and according to treatment response

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Number of units</th>
<th>Levothyroxine and liothyronine (non-responders &gt;3 months) (per year)</th>
<th>Liothyronine +levothyroxine (first 3-month trial period)</th>
<th>Liothyronine +levothyroxine (second and subsequent years in responders &gt;3 months)</th>
<th>Unit cost</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid hormone</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>100 µg daily</td>
<td>50 µg daily</td>
<td>50 µg daily</td>
<td>£16.03 per year</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Liothyronine</td>
<td>17 µg daily</td>
<td>17 µg daily</td>
<td></td>
<td>£3365.82 per year</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Healthcare professional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrinologist outpatient</td>
<td></td>
<td>3.13 (2.47)</td>
<td>2.38 (2.31)</td>
<td>2.56 (1.29)</td>
<td>£164 per visit</td>
<td>27</td>
</tr>
<tr>
<td>General practitioner</td>
<td></td>
<td>5.56 (3.11)</td>
<td>1.81 (1.85)</td>
<td>2.44 (1.24)</td>
<td>£37.40 per visit</td>
<td>43</td>
</tr>
<tr>
<td>Phlebotomist</td>
<td>5.94 (6.00)</td>
<td>4.88 (6.51)</td>
<td>5.00 (6.22)</td>
<td>£3.04 per sample</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Thyroid tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>5.94 (6.00)</td>
<td>4.88 (6.51)</td>
<td>4.81 (6.32)</td>
<td>£2.15 per test</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Free T4</td>
<td>5.94 (6.00)</td>
<td>4.88 (6.51)</td>
<td>5.00 (6.22)</td>
<td>£2.10 per test</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Free T3</td>
<td>1.25 (1.60)</td>
<td>2.50 (2.33)</td>
<td>2.56 (1.68)</td>
<td>£3.12 per test</td>
<td>16</td>
<td></td>
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<tr>
<td>TRAb antibody testing</td>
<td>0.25 (0.46)</td>
<td>0.38 (0.52)</td>
<td>0.56 (0.90)</td>
<td>£16.64 per test</td>
<td>16</td>
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<tr>
<td>TPO antibody testing</td>
<td>0.68 (0.70)</td>
<td>0.62 (0.74)</td>
<td>0.63 (0.74)</td>
<td>£12.32 per test</td>
<td>16</td>
<td></td>
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<tr>
<td>Safety monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>0.09 (0.08)</td>
<td>0.63 (0.52)</td>
<td>0.63 (0.52)</td>
<td>£58 per test</td>
<td>27</td>
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<td>Echocardiogram</td>
<td>0.09 (0.08)</td>
<td>0.63 (0.52)</td>
<td>0.63 (0.52)</td>
<td>£97 per test</td>
<td>27</td>
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<td>Bone densitometry</td>
<td>0.09 (0.08)</td>
<td>0.31 (0.46)</td>
<td>0.06 (0.07)</td>
<td>£77 per test</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SD). TSH, thyroid stimulating hormone.
the ICER, increasing to £20816 per QALY gained if only 5% of patients respond. The key driver of cost-effectiveness was the price of liothyronine. The multivariate sensitivity analysis (online supplemental appendix figure S2) illustrates the combinations of prices and effectiveness probabilities of liothyronine/levothyroxine combination therapy that result in ICERs that are cost-effective. For example, based on a 5% chance of treatment response, liothyronine/levothyroxine is cost-effective up to a cost of £3245 per annum (which is marginally less than the current annual cost of £3366).

**Probabilistic sensitivity analysis**

Parameter estimates and specification of the PSA are presented in table 5, and the results are depicted as a cost-effectiveness plane and cost-effectiveness acceptability curve in figure 2. The PSA indicated the probabilities of liothyronine/levothyroxine combination therapy being cost-effective at thresholds of £20000 and £30000 per QALY, as 0.557 and 0.642, respectively. The probability of being cost-saving is 0.060, and in generating QALY gains, is 0.939.

**Value of information analysis**

Based on a £20000 per QALY threshold for cost-effectiveness, the overall EVPI per eligible patient is estimated at £2521. This is equivalent to 0.126 QALYs per person when valuing uncertainty on the QALY scale. Assuming an annual number of patients potentially eligible for liothyronine of 10000, the overall EVPI is £25206183 per year for the UK. If it is assumed that the relevance of the present analysis persists for 10 years, the overall expected value of removing decision uncertainty for the UK would in total be £252m. The EVPPI was highest for utilities in patients who remain symptomatic (£1902 per person), followed by the probability of liothyronine combination therapy being clinically effective (£328 per person). A conservative, 1-parameter (probability of treatment response) population EVSI yielded an
estimate of £3,644,000 per year for a clinical trial of 300 patients.

**DISCUSSION**

Disinvestment of many medicines considered to be low in value has proven to be difficult to achieve in practice. This is due to a number of reasons, including system factors such as a lack of funding or incentives for change, lack of skills in change management and organisational challenges for example, in relation to reimbursement. There is also patient and healthcare professional reluctance or consideration of it as a cost-saving exercise only; the belief that removal of a medicine will result in loss of benefit, or that deimplementation has greater disadvantage than to not accept a new medicine with similar value; and, in several cases, a lack of convincing evidence of no harm from withdrawal and no benefit.

In the case of liothyronine, there are disparate clinical views, high costs and a lack of robust evidence of clinical effectiveness. However, there is also a large unmet need with only unlicensed natural desiccated thyroid extract as an alternative, and a high demand from a significant minority of people with hypothyroidism who are seemingly unresponsive to levothyroxine with associated very low health-related quality of life compared with the general population. Many report dissatisfaction with

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Total 10-year costs</th>
<th>Levothyroxine monotherapy</th>
<th>Liothyronine+levothyroxine (response following 3-month trial period)</th>
<th>Liothyronine+levothyroxine (no response following 3-month trial period)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid hormone</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Healthcare professional</td>
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<td>Endocrinologist outpatient</td>
<td>£5125.00</td>
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<td>Thyroid tests</td>
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<td>TSH</td>
<td>£127.66</td>
<td>£103.47</td>
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<td>Free T4</td>
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<td>Echocardiogram</td>
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<td>Bone densitometry</td>
<td>£67.38</td>
<td>£48.13</td>
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<td>£89.75</td>
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<td>Total (undiscounted)</td>
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<td>£40560.52</td>
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<td>£9443.52</td>
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<tr>
<td>Total (discounted at 3.5% per annum)</td>
<td>£7029.74</td>
<td>£34913.22</td>
<td></td>
<td>£8306.54</td>
</tr>
</tbody>
</table>

TSH, thyroid stimulating hormone.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Incremental costs, QALYs and cost-effectiveness ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liothyronine+levothyroxine</td>
</tr>
<tr>
<td>Costs (deterministic)</td>
<td>£19,082.25</td>
</tr>
<tr>
<td>Costs (probabilistic)</td>
<td>£18,990.83</td>
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<tr>
<td>QALYs (deterministic)</td>
<td>5.559</td>
</tr>
<tr>
<td>QALYs (probabilistic)</td>
<td>5.638</td>
</tr>
<tr>
<td>ICER (deterministic)</td>
<td>£11,880.65 per QALY</td>
</tr>
<tr>
<td>ICER (probabilistic)</td>
<td>£10,984.02 per QALY</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
treatment and experience symptoms consistent with overt hypothyroidism, including fatigue, memory problems, cognitive dysfunction, feeling cold and weight gain.\textsuperscript{3, 34} Our survey indicated their mean utility value is 0.53 which makes these individuals comparable in terms of their health status, to patients with lung cancer, or acute cerebrovascular disease and would rank in the bottom decile of 100 chronic diseases.\textsuperscript{35}

The economic analysis suggests that liothyronine/levothyroxine combination therapy may represent a cost-effective treatment option for patients who remain symptomatic with levothyroxine alone despite achieving free T4 and TSH concentrations within the reference ranges. At £11 881 per QALY gained, the ICER fell below the effectiveness threshold of £20 000 per QALY. However, the probability of liothyronine/levothyroxine combination therapy being cost effective at this threshold was 0.557, reflecting the uncertainty that continued use results in positive net health benefit.

To address the uncertainty in the clinical effectiveness of liothyronine/levothyroxine combination therapy, the analysis quantified the value of conducting research, such as a definitive randomised controlled clinical trial. In monetary terms, and based on a population EVSI of £3.64 m per year, the value of a clinical trial would be expected to exceed its cost within 1 year.\textsuperscript{36}

Literature searches did not identify any health utility measurement\textsuperscript{20} or economic evaluations of liothyronine. Judgements on its cost-effectiveness in the UK appear to be made implicitly in policy guidelines, driven in large part by the significant difference in the current unit acquisition cost between liothyronine and levothyroxine. Guidelines either consider liothyronine/levothyroxine combination therapy to be non-inferior to levothyroxine alone (based on the available weak clinical evidence), or to be inferior because of the shorter pharmacokinetic elimination half-life and safety concerns. Neither perspective is fully justified, as the current evidence base is not targeted to the specific population in question, and inferiority has not been demonstrated. Certainly, the pharmacokinetics of levothyroxine support more convenient, once daily dosing and stable concentrations of free T3. Liothyronine, by contrast, requires frequent daily dosing which causes fluctuations in free T3 that may result in transient suppressive effects on TSH.\textsuperscript{37} Although suppression of TSH (<0.03 mU/L) is associated with an increased risk of adverse cardiovascular outcomes\textsuperscript{38} and mortality,\textsuperscript{18} a case–control study of patients taking long-term liothyronine found no evidence of additional risk of atrial fibrillation, cardiovascular disease or fractures,

\begin{table}[h]
\centering
\caption{Results of one-way sensitivity analyses} 
\begin{tabular}{|l|c|c|}
\hline
Parameter & Estimate\textsuperscript{*} & ICER (£ per QALY gained) \\
\hline
Probability of response & 0.05 & £20 816.64 \\
 & 0.1 & £15 719.35 \\
 & 0.2 & £13 170.70 \\
 & 0.6 & £11 471.61 \\
Discount rate (costs) & 0% & £13 681.24 \\
 & 6% & £10 838.31 \\
Discount rate (QALYs) & 0% & £10 300.84 \\
 & 6% & £10 342.21 \\
Discount rate (costs and QALYs) & 0% & £11 862.00 \\
 & 6% & £11 897.95 \\
Time horizon (years) & 1 & £16 027.34 \\
 & 5 & £11 754.63 \\
Cost of liothyronine (per annum) & £100 & £179.10 \\
 & £1000 & £3403.83 \\
 & £10 000 & £35 651.14 \\
Utility in symptomatic state based on EQ-VAS & 0.493 & £10 544.94 \\
\hline
\end{tabular}
\textsuperscript{*}Base-case values are: probability of response 0.405, discount rate (costs and QALYs) 3.5% per annum, time horizon 10 years, cost of liothyronine £3365.82 per year and utility in symptomatic state 0.53.

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
\end{table}

\begin{table}[h]
\centering
\caption{Parameter values for the probabilistic sensitivity analysis and value of information analysis} 
\begin{tabular}{|l|c|c|}
\hline
Parameter & Mean (SD) & Distribution/notes \\
\hline
Utility & & \\
Asymptomatic (age 45–54) & 0.85 (0.25) & ~Beta (1.626, 0.287) \\
Asymptomatic (age 45–54) & 0.80 (0.26) & ~Beta (1.765, 0.441) \\
Symptomatic & 0.53 (0.23) & 1−~gamma (4.136, 0.114) \\
Survival probability & & \\
Age 45–54 & 0.9846 & Fixed \\
Age 55–64 & 0.9769 & Fixed \\
Resource use (non-drug) & Mean (SD)* & ~Beta (0.242, 0.356) \\
 & & \\
Probability of response & 0.405 (0.389) & \\
Eligible incident population (per year) & 100 000 & Based on 3% of the UK population (66.65 m) having hypothyroidism, and 5% of these not responding sufficiently to levothyroxine alone \\
Uptake of liothyronine (per year) & 10% & Assumption \\
Size of future clinical trial (n) & 300 & Assumption \\
\hline
\end{tabular}
\textsuperscript{*See table 1 for values.}
\end{table}
following adjustment for age. The TSH concentrations of these patients were within normal range (median 1.07 mU/L).

Our analysis had strengths in addressing a decision problem which is pertinent to the NHS across the UK. Generalisability to other countries might be limited, however, as the cost of liothyronine is highly variable (eg, 28 tablets costs €2.30 in Greece, €3.90 in Portugal and €36 in The Netherlands). The methods are nonetheless applicable in other jurisdictions in cases of price inflation because of monopoly supply of an off-patent medicinal product, or when medicines are presumed to be of low value because of uncertainty in their clinical effectiveness. A value of information analysis in these contexts will help inform whether there is value in reducing uncertainty (eg, by investing in further research), or whether disinvestment is more appropriate. In acknowledging the limited evidence-base, we undertook a systematic approach to populate the model when direct evidence was not available. In particular, the analysis of responses to the survey of clinicians aimed to reflect the diversity of opinions in routine care, and not to achieve consensus, consistent with accepted methods. There is considerable polarity in the views of prescribers with regards to the perceived benefits of liothyronine in the UK, and this was reflected in our analysis. While the mean probability of treatment response was 0.40, 38% of simulations had probabilities <0.1, and 20% >0.9.

However, there are caveats to our analysis. First, the model is a simple representation of what is a complex clinical management problem. Patients may often be misdiagnosed or have comorbidities and experience multiple referrals, investigations and treatments. The decision analysis assumes patients are identified and eligible at the point of entry to the model. We further assumed that responders to liothyronine/levothyroxine combination therapy would experience the same population norm health utilities as patients who are treated successfully with levothyroxine. Second, we did not consider the influence of deiodinase 2 (DIO2) genetic polymorphisms. The CC genotype (rs225014) is a purported predictor of response to combination therapy; however, this observation was based on a post hoc analysis, and has not been replicated in further studies. Third, our reliance on clinical opinions for estimates of resource utilisation may bias the analysis. Access to routine health administration data or estimates from clinical trials may be preferred, but these were unavailable. Responses to patient questionnaires may be biased for different reasons (eg, self-selection, recall bias, lack of understanding of medical procedures and terminology). Finally, our surveys of patients and clinicians were potentially limited in terms of selection bias and alternative sampling methods may have been more reliable, although we are unaware of any evidence to suggest that patient-reported resource use is more accurate than clinician-reported.

In conclusion, HTR provides a basis for informing important decisions concerning disinvestment, not only in relation to continued use, but also in relation to the value of conducting further research. It is widely appreciated that the deimplementation of low value medicines is more challenging than implementing new treatments, even when there are significant uncertainties surrounding their clinical effectiveness. In the case of liothyronine, our analysis suggests that while it might represent a cost-effective treatment option for patients who remain symptomatic with levothyroxine alone, a definitive clinical trial is necessary to confirm clinical effectiveness. This would be justified on the basis that the value of the information gained far exceeds the cost of a trial.

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their part. The AWTTIC did not input into the manuscript and are neutral with respect to the conclusions.

**Contributors** DAH conceived and designed the work, performed the analyses and drafted the manuscript. DAH, KS, and AH made substantial contributions to the acquisition of data. DAH, KS, DF, PA, AH made substantial contributions to the interpretation of data for the work; revised the manuscript critically for important intellectual content; gave their final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DAH will act as guarantor, and accepts full responsibility for the finished work, the conduct of the study, had access to the data, and controlled the decision to publish.

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**Ethics approval** Recruitment to the utility survey was done following approval by the Research and Development Department at Salford Royal Hospital after confirmation with the Greater Manchester West Ethics Committee that this was a quality improvement exercise. The survey of health care professionals did not require ethical approval.

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**Data availability statement** Data are available upon reasonable request.

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