National Institute for Health and Care Excellence

Final

Thyroid cancer: assessment and management

Cost-utility analysis: recombinant human thyroid stimulating hormone (rhTSH) versus thyroid hormone withdrawal in people in preparation of Radioactive Iodine Ablation (RAI)

NICE guideline NG230

Economic analysis report

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Final

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Contents

1 Introduction

With radioactive iodine ablation (RAI), people receive a radioactive substance called iodine-131 usually administered in capsules. The radioactive substance is then absorbed by the thyroid tissues destroying them in the process. This therapy is commonly given to people who underwent total thyroidectomy due to a diagnosis of differentiated thyroid cancer (DTC) to ablate any remaining cancerous or thyroid tissues after surgery.

To increase Iodine-131 uptake, a high level of thyroid stimulating hormone (TSH) is required. This was historically achieved by suspending thyroid hormone replacement treatment for a period of 2-4 weeks to force a state of hypothyroidism. This increases the level of TSH produced by the body but at the same time adversely affects quality of life for the duration of the withdrawal. In recent years, however, TSH has been artificially created in the laboratory and given to patients through an intramuscular injection. This recombinant human TSH or rhTSH is currently available in the UK as Thyrotropin Alfa (TA) and does not require any thyroid hormone withdrawal thus avoiding quality of life harms associated with hypothyroidism.

The clinical review included three randomised controlled trials (RCTs)[14, 23, 24] comparing rhTSH and thyroid hormone withdrawal (THW) in people receiving RAI. The review found no differences in clinical outcomes such as mortality, recurrence and successful ablation between the two strategies. However, both SF-36 and EQ-5D utility measures found a statistically and clinically significant difference in quality of life at time of ablation where people in the THW group scored worse both in physical and psychological components.

Four studies were included in the health economics literature review although a clear conclusion could not be drawn. In particular, it was observed that the three studies[15, 25, 27] based on the first RCT Pacini 2006[23] found rhTSH cost effective whereas a more recent study[6] based on the latest Estimabl[24] trial found rhTSH not cost effective against THW. This reflects the difference in trial outcomes as Pacini 2006 found a severe quality of life harm with THW whereas Estimabl and HiLo found a much smaller though still significant difference. Thyrotropin Alfa is a relatively expensive drug with a BNF price of £583. Considering that around 2,500 RAI are performed each year according to the NHS Reference Costs 2019/2020, rhTSH represent a large use of NHS resource. The potentially large resource use and the uncertainty surrounding previous published economic analyses strongly justified the need of an original economic evaluation, using NHS price and all the available evidence instead of single trials to estimate quality of life. A quality of life simulation model with a time horizon of 4 months and half was developed and used to estimate costs and quality of life to determine the most cost-effective intervention.

2 Methods

2.1 Model overview

A cost-utility analysis was undertaken with quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective were considered. The analysis followed the standard assumptions of the NICE reference case for interventions with health outcomes in an NHS setting[16]. The time horizon of the model was limited to 4½ months, as beyond this point no difference in quality of life or survival was observed. An incremental analysis was undertaken.

2.1.1 Comparators

The following comparators were included in the analysis:

1. Recombinant human TSH (rhTSH) with Thyrotropin Alfa (TA)
2. Thyroid hormone withdrawal (THW)

2.1.2 Population

The population of the analysis was adults in preparation for radioactive iodine ablation (RAI).

2.2 Approach to modelling

A simple quality of life simulation model was developed to assess the cost effectiveness of rhTSH compared to THW. The temporary utility deterioration caused by withdrawal and the lack of differences between clinical long-term outcomes such as mortality and recurrence did not justify the development of more complex lifetime models. Based on clinical evidence, the analysis assumes that the only differences in the two strategies are healthcare costs and quality of life during the four and half months of the time horizon. Beyond this point, no difference is expected to occur between the groups.

2.2.1 Model structure

A quality-of-life simulation model of 9 cycles, with each cycle corresponding to a half-month, was developed. A description of the structure of the model is presented in Table 1.

Withdrawal is assumed to occur at the end of the first cycle as in the previous half-month a proportion of people switch to T3 for a period of 2 weeks beforehand. Once withdrawal starts, quality of life starts to decrease as a consequence of withdrawal-induced hypothyroidism. At the end of cycle 2, withdrawal ends and people receive RAI. From cycle 3 onward, replacement therapy is resumed with T4 (in the base case scenario) and quality of life begins to improve. By cycle 9, quality of life reaches the same level as that of people in the rhTSH strategy who did not undergo withdrawal. From that month onwards, no difference is expected in the two groups.

People in the rhTSH strategy never undergo withdrawal and receive RAI and rhTSH together in cycle 1. During the entire duration of the model they are assumed to be treated with T4.

A half-cycle correction was applied to calculate QALYs. A comparison of costs and QALYs accrued during the 9 cycles of the model allowed us to calculate cost per QALY of rhTSH compared to THW.

Table 1: Model structure

Month	THW	rhTSH

Month	THW	rhTSH
0	A proportion of people receiving T4 are switched to T3 before the start of withdrawal	People receive T4 as part of their thyroid hormone replacement therapy
0.5	Withdrawal starts. T4 and T3 medication are stopped. Quality of life starts to decrease.	People receive rhTSH and RAI. T4 treatment is not interrupted.
1	Withdrawal ends. People receive RAI at the end of the cycle.	People receive T4 as part of their thyroid hormone replacement therapy
1.5	Thyroid hormone replacement therapy is resumed with T4. Quality of life starts to improve	People receive T4 as part of their thyroid hormone replacement therapy
…	…	…
4.5	Quality of life reaches pre-withdrawal level and there is no difference with rhTSH	People receive T4 as part of their thyroid hormone replacement therapy

2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for two base case scenarios– and results were summarised.

The way in which distributions are defined reflects the nature of the data, so for example event probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that the probability of an event occurring cannot be less than 0 or greater than 1. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 2 and in the relevant input summary tables in section 2.3.1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 2: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
SF-36 dimension score	Beta	Bounded between 0 and 1. SF-36 dimension scores are bounded between 0 and 100 so they were divided by a factor of 100. Derived from mean and its standard error, using the method of moments. Alfa and Beta values were calculated as follows: Alfa = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = $alfa \times [(1-mean)/mean]$
Changes in SF-36 dimension score	Normal	Symmetric from the peak of the curve with most of the observed data clustered near the mean. It is unbounded and it was used not to contain direction of change.
Parameters of mapping algorithm	Normal	Symmetric from the peak of the curve with most of the observed data clustered near the mean. It is unbounded and it was used not to contain direction of change.
Probability of GP/specialist/hospital	Beta	Bounded between 0 and 1. As the sample size and the number of events were specified alfa and beta values

Parameter	Type of distribution	Properties of distribution
attendance		were calculated as follows: • Alfa = (number of patients hospitalised) • Beta = (number of patients) − (number of patients hospitalised)
Dosage of T4 thyroid hormone replacement	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard error. Alfa and beta values were calculated as follows: • Alfa = (mean/SE)2 • Beta = SE2/Mean

Abbreviations: 95% CI = 95% confidence interval; SE = standard error; SMR = standardised mortality ratio.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- Healthcare costs (assumed to be fixed and based on unit costs from UK national sources)
- Drug prices
- Proportion of people taking T3 and T4, as its impact was explored in the deterministic sensitivity analysis
- England population data such as weight that was informed from national statistics (ONS)

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. Details of the sensitivity analyses undertaken can be found in methods section 2.4 Sensitivity analyses.

2.3 Model inputs

2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the guideline committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 3 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 3: Overview of parameters and parameter distributions used in the model

Input	Data	Source	Probability distribution
Comparators	• rhTSH • THW		n/a
Population			n/a
Perspective	UK NHS & PSS	NICE reference case[16]	n/a
Time horizon	4.5 months		n/a
Cohort settings			
Age	50 years	Assumed, BAETS[26]	Fixed
% of females	79%	BAETS 2021[26]	Beta
Weight female	70.2kg	ONS[22]	Fixed
Weight male	83.6kg	ONS[22]	Fixed
% switching to T3	57.1%	Calculated from	Fixed

Input	Data	Source	Probability distribution
in the 2 weeks prior withdrawal		Estimabl[24]	
Resource use with withdrawal			
Hospital attendance	29%	Luster 2005[12]	Beta
1 GP attendance	18%	Luster 2005[12]	Beta
2 GP attendances	20%	Luster 2005[12]	Beta
1 specialist visit	19%	Luster 2005[12]	Beta
2 specialist visits	12%	Luster 2005[12]	Beta
Health-related quality of life			
rhTSH EQ-5D	Baseline: 0.83 At ablation: 0.81	Pacini 2006[23], Estimabl[24], HiLo[13] mapped into EQ-5D using Ara and Brazier 2008[1]	Beta, normal
THW EQ-5D	Baseline: 0.84 At ablation: 0.88	Pacini 2006[23], Estimabl[24], HiLo[13] mapped into EQ-5D using Ara and Brazier 2008[1]	Beta, normal
Costs			
Thyrotropin alfa (2 doses)	£583	NHS Indicative Price [5]	Fixed
T3 price per mg	£117	Drug Tariff[19]	Fixed
T4 price per mg	£0.96	BNF[5], PCA [10]	Fixed
Dosage T3 (mg)	0.060	BNF[5]	Fixed
Dosage T4 (mg)	0.117	Calculated from Banovac [2]	Gamma
RAI outpatient	£433	NHS Reference Costs 2019-2020[21]	Fixed
Excess bad day cost	£303	NHS Reference Costs 2017-2018[20]	Fixed
GP visit	£33	PSSRU 2020[9]	Fixed
Endocrinology attendance	£151	NHS Reference Costs 2019-2020[21]	Fixed
Outpatient for thyroid disorder	£203	NHS Reference Costs 2019-2020[21]	Fixed
LOS			
rhTSH	2.4	Borget 2015[6]	Fixed
THW	2.2	Borget 2015[6]	Fixed

Abbreviations: LOS = Length of Stay; mg = milligram; rhTSH = Recombinant Human Thyroid Stimulating Hormone; TSH = Thyroid Stimulating Hormone; THW = Thyroid Hormone Withdrawal.

2.3.2 Quality of life at ablation

Estimabl[24] and Pacini 2006[23] reported SF-36 scores at ablation and baseline whereas HiLo[13] reported only incremental values (see Appendix A:). Ablation, which usually occurs 4 weeks after beginning withdrawal, reflects the lowest quality of life of people in THW group as it is the last observation before thyroid hormone replacement is resumed. After RAI is administered, people are allowed to resume their medication and their quality of life rapidly

improve to pre-withdrawal levels. Therefore, it is expected that this point in time reflects the largest difference in quality of life between the two strategies.

SF-36 components scored were mapped into EQ-5D utility scores using the mapping algorithm from Ara and Brazier 2008[1]. The algorithm's parameters were estimated assuming a normal distribution around the mean and using standard errors provided by Ara & Brazier[1]. The resulting EQ-5D scores at ablation and baseline are illustrated in Table 4 together with the difference at ablation adjusted for differences at baseline. Baseline quality of life was not available in the HiLo trial so an average of baseline EQ-5D values of Pacini and Estimabl was used instead. The values at ablation were calculated using the clinical meta-analysis (see Appendix A:). Meta-analysed SF-36 domains were again mapped into EQ-5D scores using Ara and Brazier algorithm.

Table 4: Mapped EQ-5D and meta-analysis

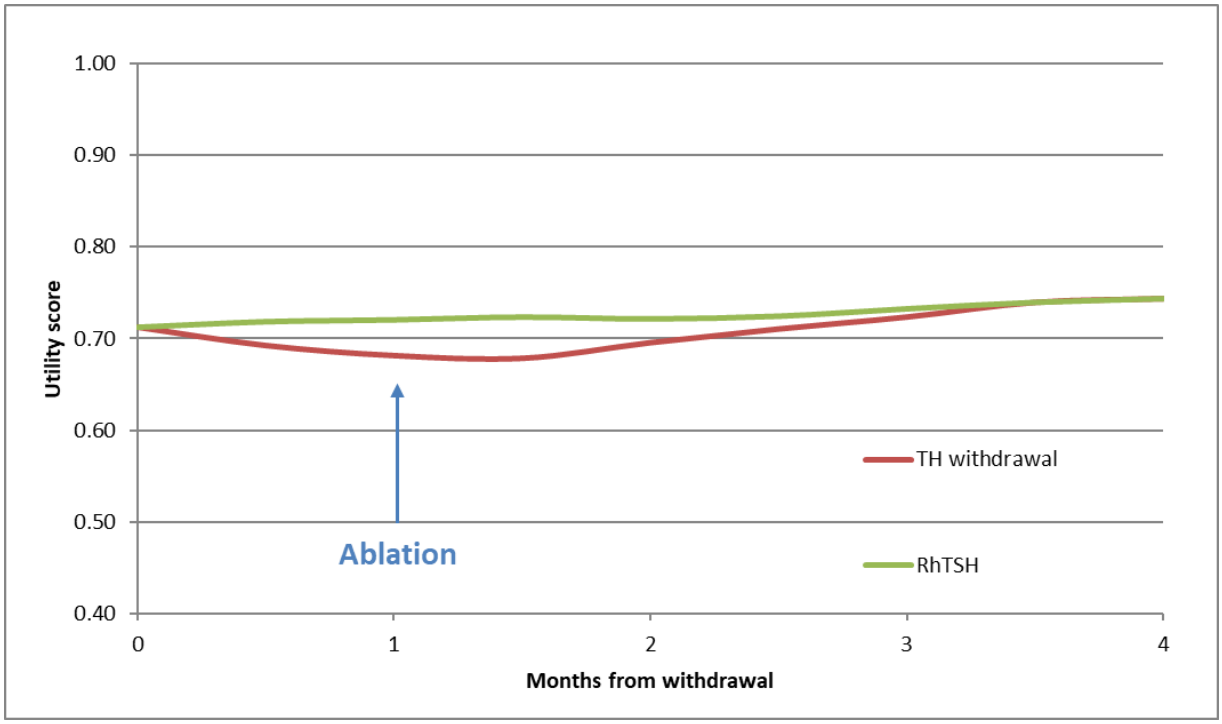
Trial	Time	THW	rhTSH	Difference at ablation (adjusted)
Pacini 2006[23]	Baseline	0.78	0.80	0.13
	Ablation	0.71	0.86	
Estimabl[24]	Baseline	0.89	0.88	0.06
	Ablation	0.84	0.89	
HiLo[13]	Baseline	0.83	0.84	0.05
	Ablation	0.81	0.87	
Meta-analysis	Baseline	0.83	0.81	0.07
	Ablation	0.84	0.88	

As mentioned before, Pacini 2006 found a much larger difference in quality of life at ablation compared to the other two studies even after correcting for baseline differences. HiLo and Estimabl reported the same difference of around 0.05 at ablation. The meta-analysed value of 0.07 was used in the base case scenario of this analysis.

2.3.3 Utility curve

Although most of the RCTs included reported only one or two data points of quality of life collected within the study, a study from Borget[6] and based on ESTIMABL trial[24], was able to collect several data points during the trial and to create two utility curves using SF-6D utility scores (see Figure 1).

Figure 1: SF-6D utility curve from ESTIMABL

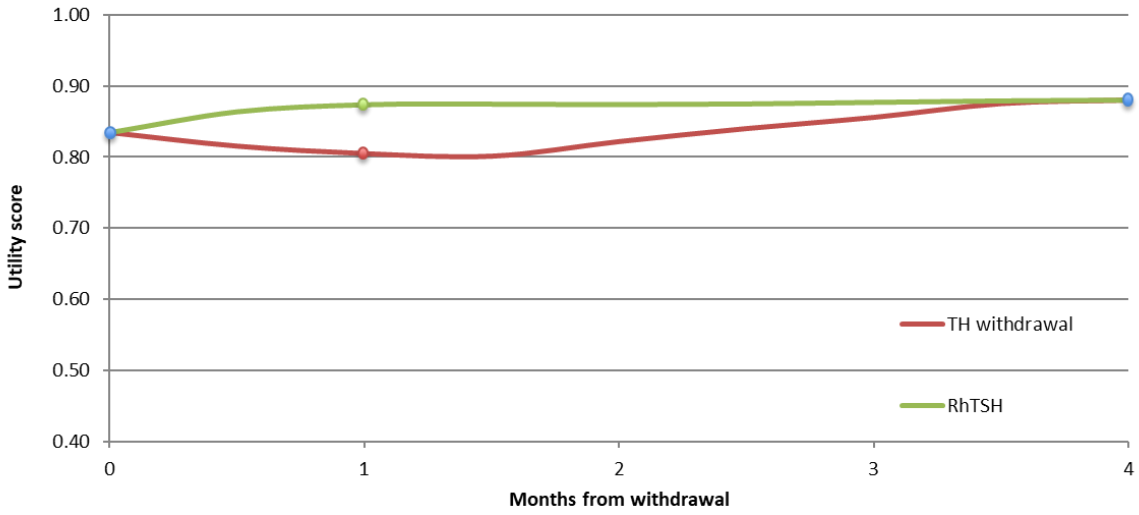


Note: Data points were extracted using Web Plot Digitizer[28]

These curves behave in a way that could be anticipated: whereas quality of life in the rhTSH group appears to be constant or to slightly increase over time, quality of life in the withdrawal group significantly decreases after the beginning of withdrawal due to the onset of hypothyroidism symptoms and appears to recover only 1 month later when RAI is supposed to take place and people resume their thyroid hormone replacement medication. By month 2, quality of life in the THW group has significantly increased but would reach the same level of rhTSH only between month 3 and 4. By month 4, no difference in quality of life is observable, which justifies the decision to limit the time horizon of the model to 4½ months.

The curves in Figure 1 represent SF-6D utility scores instead of EQ-5D and come from a single study instead of the meta-analysis. Consequently, these curves were refitted using values obtained from the meta-analysis under the assumption that the shape and the incremental changes overtime would remain the same. This was achieved in 2 steps: firstly, known EQ-5D utility scores from the meta-analysis and Estimabl (0 month, point of ablation and observed utility at 4 months) were assigned to the corresponding month (the 4 data points in Figure 2). In the second step, utility scores between known data points were estimated using the same incremental change between the same data points in the SF-6D utility curves. With this approach, the new curves maintain the same shapes of the previous ones but instead reflect EQ-5D utility scores estimated using all the available evidence (see Figure 2).

Figure 2: Utility curves refitted to use meta-analysis EQ-5D utility scores



2.3.4 Thyroid hormone replacement

Although there are two drugs commonly used as thyroid hormone replacement, Levothyroxine (T4) and Liothyronine (T3), treatment-naïve people have been predominantly prescribed T4 in recent years as a part of a strategy from the NHS to contain rising T3 costs in England (see 2.3.5).

Therefore, it is assumed that all the people withdrawing had been initially prescribed T4 post-surgery. However, Committee experience suggests that people may be switched to T3 treatment for a couple of weeks before withdrawal, because T3 has a faster body clearance, reducing withdrawal to around 2 weeks. This has important implications for the analysis as the cost of T3 in the UK is considerably higher than the cost of T4.

All the trials except Estimabl[24] enrolled people withdrawing from T4 only. Estimabl had people enrolling from either T-3 or T-4 in a proportion that was not disclosed but could be estimated by looking at their average withdrawing time: 20 days. The assumption that withdrawal after T4 lasts for 28 days and after T3 for 14 days, allowed us to calculate a rough proportion of 57% withdrawing from T3 and the remaining from T4. This proportion was used in one of the two main scenarios to calculate pharmaceutical costs. Given the unusually high cost of T3 in England, a scenario where nobody switches to T3 is presented as well (see 2.4).

At the end of the withdrawal period, everyone resumes their thyroid hormone replacement with T4. It is possible that people who had undergone withdrawal are prescribed T3 for the first 2 weeks after RAI as, similar to the clearance from the body, T3 has a faster rate of absorption and allows people to recover from hypoparathyroidism faster. This was tested in one of the scenario analyses (see 2.4).

2.3.5 Costs

2.3.5.1 Pharmaceutical costs

There are 3 main drugs involved in this analysis: T3, T4 and Thyrotropin Alfa (TA) which is the recombinant human TSH provided to people in the rhTSH strategy.

Price and dosage of T3 and T4 were estimated from the British National Formulary (BNF)[5] Drug Tariff[19] and published studies[2] whereas the Prescription Cost Analysis (PCA)[10] data

was utilized to calculate the weighting given to the different preparations. The final cost of the two drugs is presented in Table 5.

Table 5: Cost of T3 and T4 in England

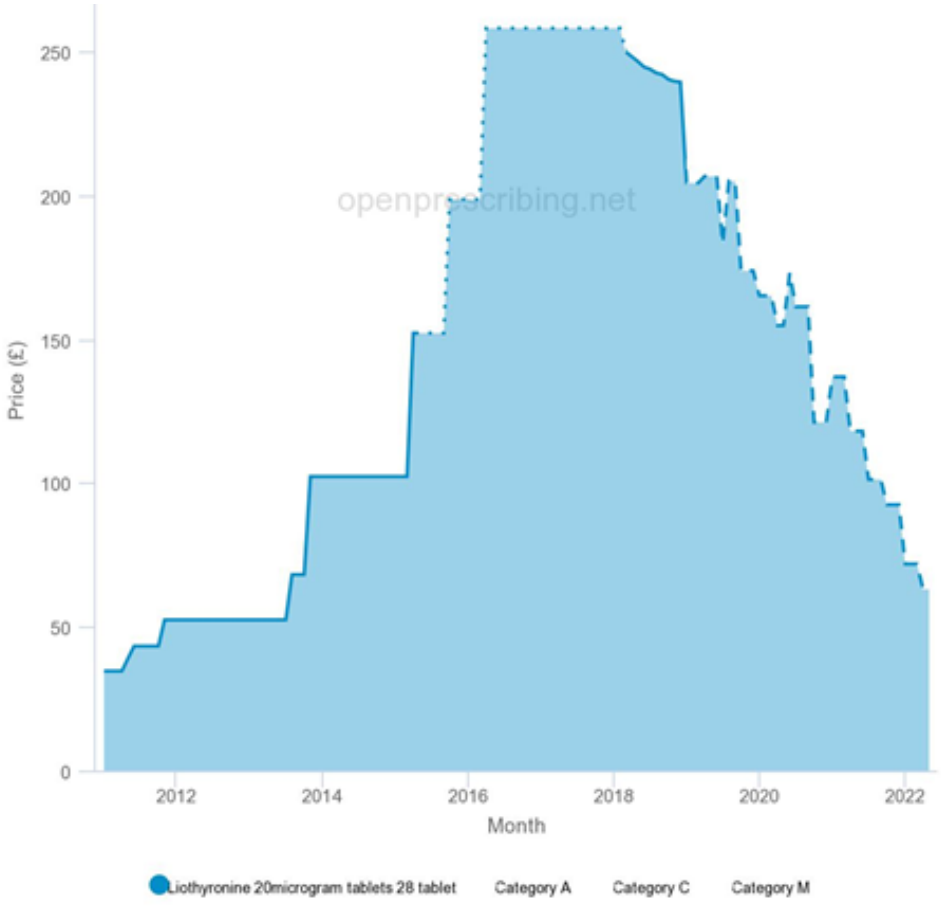
Thyroid hormone replacement	Cost per mg	Cost per day[(a)]
Liothyronine (T3)	£117	£8
Levothyroxine (T4)	£0.96	£0.12

(a) Assuming a dosage of 0.060 mg a day for T3 (BNF[5]) and 0.117 mg a day for T4[2]

Source: BNF[5], Drug Tariff[19], Banovac 1990[2] and PCA[10]

The difference in price between T3 and T4 is extremely unusual as in most European countries the two drugs are charged at the same price per mg. Historically, this was true for the UK as well until 2008, when the manufacturer gradually increased the price reaching a peak of 6,000% of the original price in 2018[3] (see Figure 3). After the beginning of an investigation from the Competition and Markets Authority (CMA)[8] that ended with a fine imposed on the pharmaceutical company in 2021 for "excessive and unfair prices"[11], the price has steadily been going down reaching in May 2022 the same price of 2014. This descending trend suggests that in the near future T3 may reach the original price of 2008 which is in line with international prices charged in European countries. For this reason, a sensitivity analysis using 2008 price for T3 was conducted (see 2.4.2).

Figure 3: Price of T3 (Liothyronine) over time in England



Source: OpenPrescribing.net[3]

The cost of two doses of Thyrotropin Alfa amount to £583 according to the NHS indicative price. The price is almost never dispensed in a primary setting and therefore the NHS indicative price was considered more reliable. To raise TSH in the body to a sufficient level

for RAI, two doses of intramuscular injection of Thyrotropin Alfa are needed and therefore the entire cost reported in the NHS indicative price was applied to people in the rhTSH strategy.

2.3.5.2 Health care utilisation with withdrawal

Committee's clinical experience suggest that a loss of utility is not the only harm or consequence caused by withdrawal as, during hypothyroidism, it is more likely for people to seek additional healthcare services. Prompted by the Committee, a survey on healthcare utilization of 130 people undergoing withdrawal-induced hypothyroidism[12] was included among the evidence to estimate additional resource use in the withdrawal strategy. The results of the survey are summarised in Table 6.

Table 6: Probability of utilisation and cost of additional healthcare service in people with withdrawal-induced hypothyroidism

Health care service	Probability of utilisation	Unit cost	Source
GP attendance	Only once: 18% Twice: 20%	£33	PSSRU[9]
Specialist attendance	Only once: 19% Twice: 12%	£151	NHS Reference Costs 2019/2020[21] HRG = WF01A
Hospital attendance	29%	£203	NHS Reference Costs 2019/2020[21] HRG = KA09E Outpatient

Unit costs in Table 6 were collected from the NHS Reference Costs 2019/2020 and PSSRU and the latter includes qualification costs too. On average, people undergoing withdrawal require additional health care services for a value of £142 during the 2-4 weeks of hypothyroidism. This represents a significant cost, though not high enough to cancel out the cost of Thyrotropin Alfa.

2.3.5.3 RAI

Radioactive iodine ablation was sought from the NHS Reference Cost under the code RN51Z: Oral Delivery of Radiotherapy for Thyroid Ablation. The national average unit cost of the procedure was £433 and it was assumed to include one day of length of stay (LOS)

It has been shown that the use of rhTSH reduces the amount of radiation people absorb during the procedure[7]. This has two important implications: firstly, a lower amount of radiation absorption is preferable as this would reduce the incidence of secondary carcinoma. Secondly, a lower radiation absorption reduces the amount of time people need to remain under observation after they receive RAI, as people would reach faster the threshold radiation level to be discharged. This latter has cost implications in terms of length of stay (LOS) cost. Estimabl trial[24] reported a mean LOS difference of 0.2 days and this was used to calculate the incremental LOS cost between the two strategies. The cost of an additional day in bed was estimated by looking at excess bed day cost of people undergoing non-surgical thyroid procedure with the lowest CC (comorbidity and complication) score using NHS Reference Costs 2017-2018 (HRG: KA07C)[20]. This is because people who received RAI waiting to be discharged are not expected to require any particular healthcare service, hence the cost of their bed day is probably reflected by the cost of people admitted in the hospital for simple non-surgical thyroid procedures.

2.4 Sensitivity analyses

2.4.1 Base case scenarios

Two base case scenarios were made fully probabilistic and presented together. In one scenario, as mentioned in section 2.3.4, it was assumed that around 50% of people received T3 instead of T4 for the two weeks before withdrawal. In the second scenario, the switch to T3 was assumed not to occur and T3 was effectively removed from the analysis. The reason to include this scenario was the disproportionate impact of adding T3 to the analysis which is caused by the unusually high price of Liothyronine in England. Were this analysis conducted in any other European country, the inclusion of T3 would have not affected the results of the analysis as T3 is commonly sold at the same price per mg as T4. If, in the future, the T3 price returns to an internationally competitive level, the second scenario would probably reflect better long-term cost effectiveness of rhTSH.

2.4.2 Scenario analysis

Additional scenario analyses were conducted to include Committee's views on the model's assumptions.

As the results of the trials were found to be heterogenous in terms of the magnitude of the effect, 4 different scenarios were tested. In one scenario, the same weight was given to each trial whereas in the other scenarios, each trial was individually used to determine the intervention effectiveness.

Other scenarios involve different assumptions on T3. In one scenario, people were assumed to resume thyroid hormone replacement with T3 instead of T4 for 2 weeks as this should speed up hypothyroidism recovery. In a further scenario, everyone was assumed to switch to T3 before initiating withdrawal. Finally, given the steady decline in price of T3 after the start of CMA investigation, a scenario using the original 2007 price was tested as well.

2.4.3 Adherence

Although all the trials included in the clinical review report no difference in adherence and a comparable TSH level before the ablation, the committee were aware that, in the real world, it is not uncommon for people on withdrawal to have a poor adherence to the treatment. In some cases, hypothyroidism symptoms can become serious enough to hinder daily life tasks, including working, which may prompt people and physicians to interrupt the withdrawal.

As data on adherence in the real world was not available, a threshold analysis on the level of adherence was conducted instead. Adherence in the model was defined as the probability that people in the withdrawal arm will present at their RAI appointment with a TSH level lower than the one required to receive ablation. When this occurs, it was assumed that they would need 2 doses of Thyrotropin Alfa before undergoing ablation. The threshold analysis was conducted in both base case scenarios to calculate the threshold level of adherence making rhTSH cost effective.

2.5 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given

inputs. The model was peer reviewed by a second experienced health economist from the National Guideline Centre; this included systematic checking of the model calculations.

2.6 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost effective if:

- ICER < Threshold

2.7 Interpreting results

NICE sets out the principles that committees should consider when judging whether an intervention offers good value for money.[16-18] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

3 Results

3.1 Base case

The probabilistic base case scenarios results are presented in Table 7.

Table 7: Probabilistic costs and QALYs[(a)]

	THW	rhTSH	rhTSH – TWH
Scenario 1			
Mean cost (95% CI)	£1,191 (£1,162 to £1,224)	£1,515 (£1,506 to £1,526)	£323 (£292 to £351)
Mean QALYs (95% CI)	0.31 (0.27 to 0.36)	0.33 (0.27 to 0.38)	0.011 (0.003 to 0.021)
Scenario 2			
Mean cost (95% CI)	£1,133 (£1,103 to £1,165)	£1,515 (£1,506 to £1,526)	£382 (£351 to £410)
Mean QALYs (95% CI)	0.31 (0.27 to 0.36)	0.33 (0.27 to 0.38)	0.012 (0.003 to 0.021)

(a) Costs and QALYs are calculated per person and averaged across 10,000 simulations.

In both scenarios, rhTSH yields a higher cost per patient than THW although, in scenario 2 where a proportion of people are assumed to switch to T3 prior to withdrawal, the difference in cost is smaller.

The probabilistic cost-effectiveness results are presented in Table 8.

Table 8: Probabilistic cost-effectiveness results

rhTSH vs THW	Scenario 1	Scenario 2
Cost per QALY	£27,315	£32,330
Probability rhTSH cost effective at £20,000 threshold	18%	7%
Probability rhTSH cost effective at £30,000 threshold	59%	43%

The probabilistic cost per QALY is below the £30,000 threshold in the scenario 1 and rhTSH has a probability of being cost effective at £20,000 and £30,000 thresholds of, respectively, 18% and 59%.

In scenario 2, cost per QALY is beyond both £20,000 and £30,000 thresholds and the probability that rhTSH is cost effective decreases to 7% and 43% at £20,000 and £30,000 thresholds respectively.

3.2 Sensitivity analyses

3.2.1 Scenario analysis

Several one-way sensitivity analyses were conducted as mentioned in section 2.4. The deterministic results are illustrated in Table 9.

Table 9: Deterministic scenario analyses results

	Incremental cost	Incremental QALYs	Cost per QALY

	Incremental cost	Incremental QALYs	Cost per QALY
Scenario 1 (probabilistic)	£323	0.012	£27,315
Scenario 2 (probabilistic)	£382	0.012	£32,330
Give T3 to people for 2 weeks after withdrawal	£164	0.012	£13,914
Everyone switches to T3 before withdrawal	£279	0.012	£23,635
Equal weight to each trial	£323	0.014	£22,769
Utilities based on Pacini 2006	£323	0.023	£13,776
Utilities based on ESTIMABL	£323	0.012	£27,562
Utilities based on HiLo	£323	0.009	£35,570
SF-6D utility score (ESTIMABL only)	£323	0.007	£48,777
2007 price for T3	£378	0.012	£32,021

rhTSH becomes cost effective at a £20,000 threshold when it is assumed that people would receive T3 for 2 weeks after withdrawal and in the scenario where utilities were estimated using Pacini 2006 trial[23] only. This is in line with previous studies based on Pacini finding rhTSH to be extremely cost effective (see discussion in section 214.4).

When utility estimation was based entirely on more recent trials such as HiLo or ESTIMABL, cost per QALY was found to increase. In addition, when the price of T3 was assumed to be equal to its original price in 2007 (£4)[8], cost per QALY was found to be very similar to scenario 1, above the £30,000 threshold.

3.2.2 Threshold analysis

As mentioned in section 2.4.3, a threshold analysis on adherence in the THW group was conducted. Adherence following withdrawal was defined as the probability of people to show up at RAI appointment with an insufficient TSH level. In this case, they are assumed to require rhTSH before receiving RAI. In the base case scenarios adherence was assumed to be 100%. In the threshold analysis, the threshold of adherence was the level of adherence at which rhTSH switches to being cost effective. The results are illustrated in Figure 4 and Figure 5.

Figure 4: Threshold analysis on adherence in THW group (scenario 1)

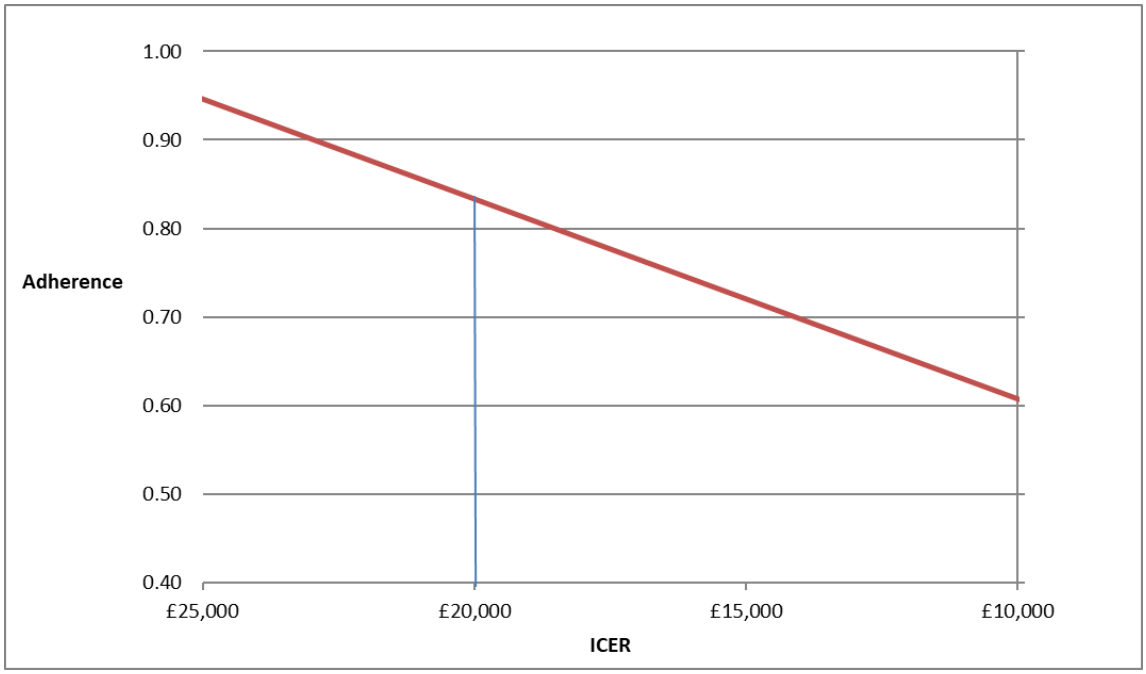
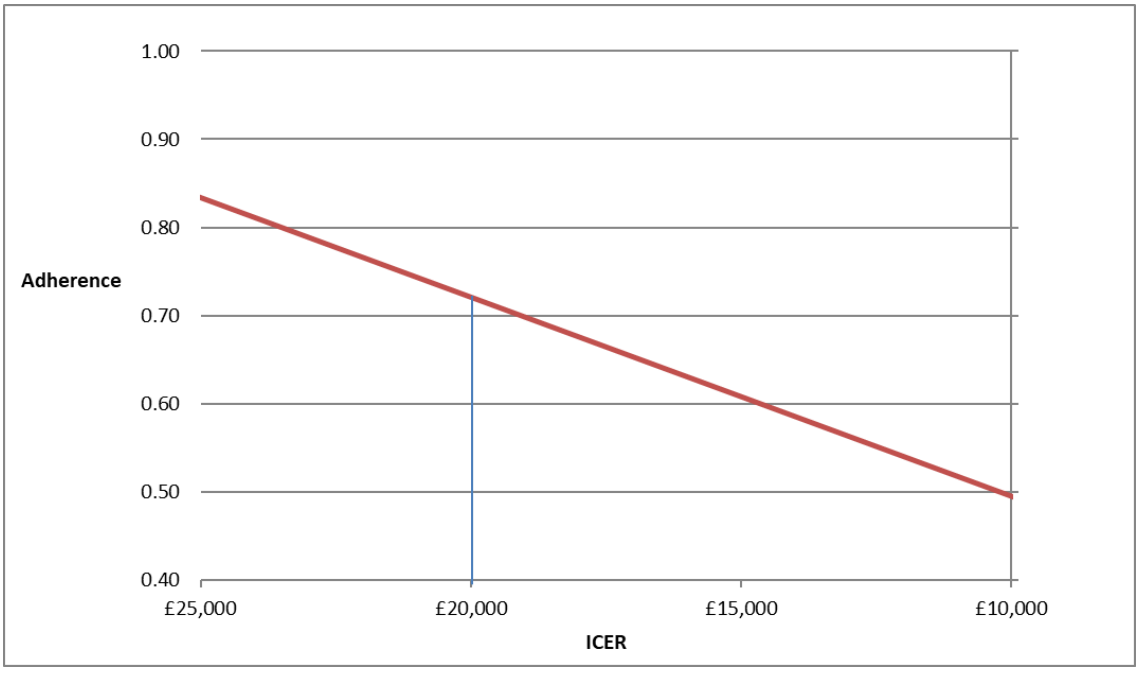


Figure 5: Threshold analysis on adherence in TWH group (scenario 2)



The threshold analyses showed that if adherence is below 85%, meaning that for every 10 patients undergoing withdrawal between one and 2 do not entirely comply with withdrawal, then rhTSH becomes cost effective at a threshold of £20,000 in scenario 1. In scenario 2, rhTSH becomes cost effective at £20,000 thresholds when adherence goes below 75%.

4 Discussion

4.1 Summary of results

This original cost-utility analysis found that rhTSH is potentially cost-effective compared to THW at a threshold of £30,000. RhTSH was found to be not cost-effective if the impact of the unusually high T3 price in England was removed from the analysis. This analysis was assessed as directly applicable with minor limitations.

4.2 Limitations and interpretation

The analysis demonstrated that rhTSH may be potentially cost effective in England but only at a £30,000 threshold. By comparing Scenario 1 and Scenario 2 it becomes clear that a large part of the cost-effectiveness of rhTSH in Scenario 1 is driven by the assumption about the higher usage of T3 in Scenario 1. The cost of T3 in England is at present extremely high and its price unusual compared with the price in other countries. For instance, the cost per unit of T3 in Germany is around £0.26[4] compared to a cost of £3.62 in the UK, which has prompted many people to purchase the drug from abroad. The reasons for the unusual price were discussed in section 2.3.5.1 and a legal process is ongoing. The price has been steadily declining since the start of the investigation in 2019 (see Figure 3) and it is possible it will reach the original price of £4 in the future. If this happens, the sensitivity analysis shows that the cost per QALY would be similar to Scenario 1, above £30,000. It is also possible that with the reduction of T3 price, NHS prescribers will start offering T3 more often to people undergoing thyroid hormone replacement therapy or preparing for withdrawal. As withdrawal from T3 is generally less harmful and shorter, this may improve quality of life of people undergoing THW which would make the alternative rhTSH less cost-effective.

In addition to the price of T3, the cost per QALY was found to be very sensitive to the level of adherence in the THW group. The trials included in the clinical review did not find any difference in terms of adherence and TSH level at ablation. However, it was acknowledged that randomised controlled trials often fail to observe the level of treatment adherence that would occur in a real-world scenario. Withdrawal-induced hypothyroidism often drastically hinders and limits important daily life activities, including work. This was confirmed by both physicians and patient representatives in the Committee. Consequently, it is not rare, in clinical practice, to see people on withdrawal with a level of TSH insufficient to receive RAI due to low compliance. In this scenario, they often receive one or two injections of rhTSH before undergoing ablation. This was explored in the threshold analysis on adherence level in the THW group as real-word data were not available. The threshold analysis showed that a small reduction in adherence (10%) was enough to make rhTSH cost-effective at £20,000 threshold in Scenario 1. Adherence was also pivotal in Scenario 2, as 5% of its reduction was enough to make rhTSH cost-effective at £30,000 but a much larger reduction of 25% was necessary to reach cost-effectiveness at a threshold of £20,000.

The three trials included in this analysis were found to be heterogenous in determining the magnitude of rhTSH effectiveness. Pacini 2006[23] found the largest difference in terms of QALYs (0.023) which explains why all economic analyses based on this trial found rhTSH to be extremely cost-effective (see discussion in section 4.4). The other trials, ESTIMABL[24] and HiLo[13], generally found a much lower QALY difference, 0.009 and 0.012 respectively, but only one published economic analysis was found using ESTIMABLI[6]. The analysis found rhTSH not cost-effective and prompted the development of this original analysis based on a meta-analysis of all three trials. It is unclear why utility estimation in Pacini 2006[23] was so different from the estimations of more recent trials. It is possible that, being older than the other two, people in THW were manged in a less optimal way, thus decreasing their quality of life. Moreover, all people undergoing THW in Pacini 2006 withdrew exclusively from T4 whereas in more recent trials a proportion of people withdrew from T3 instead. As T3 is

known to reduce the duration and harm of withdrawal, it is not surprising that more recent trials found less harm with THW.

There are some limitations in this analysis. Firstly, this analysis was conducted from a healthcare perspective only and, as such, excluded all personal and societal costs borne by individuals. These are particularly significant in people undergoing hypothyroidism as, in many cases, they are not able to perform most daily activity including working. The impact of this would be disproportionally borne by people belonging to low socio-economic groups with low paid jobs or zero-hour contract as they would find themselves without a stable income during the weeks of withdrawal.

Secondly, the committee were aware of local inefficiencies in the delivery of RAI to people undergoing withdrawal that may increase the duration of withdrawal more than intended and therefore increasing harms on quality of life caused by withdrawal-induced hypothyroidism. Moreover, a change in current practice towards an increased use of withdrawal may further disrupt NHS providers and prolong waiting time for RAI, which may lead to more people developing persistent or recurrent disease due to a late ablation of thyroid issue. The extent of this disruption could not be directly included due to lack of data.

Finally, rhTSH had other healthcare and societal advantages that could not be estimated with this analysis. RhTSH was shown to reduce radiation absorption during RAI and to allow faster radiation clearance from the body after RAI[7]. A lower radiation exposure has undeniable benefits for the society and the NHS as it would reduce the number of secondary malignancies occurring later. However, the benefits of a reduced radiation exposure could not be incorporated in the analysis due to the limited availability of data and, consequently, the analysis may underestimate the real cost-effectiveness or rhTSH.

4.3 Generalisability to other populations or settings

The results of Scenario 1 of this analysis are not generalisable to other countries due to the peculiar price of T3 in England, which plays a major role in the cost-effectiveness of rhTSH in England. It is expected, therefore, that if the analysis was repeated in another country where prices or T3 and T4 are comparable, rhTSH would be less cost-effective with a cost per QALY higher than £30,000 similarly to Scenario 2.

The population of this analysis was adults preparing for RAI after a total thyroidectomy. It is important to note that people may receive rhTSH for reasons other than preparation for RAI. For instance, TSH test which is a blood test routinely conducted in follow-up visits to control recurrence, is sometimes performed after stimulating TSH either through rhTSH or withdrawal. As this analysis focused on differences in quality of life between rhTSH and THW, the same conclusions may be applied to people whose TSH is being stimulated for the blood test instead of RAI. However, although published evidence seems to show no difference in RAI effectiveness between the two strategies, which justifies the scope of this analysis being limited to short-term quality of life, it is not certain whether stimulated TSH tests with withdrawal or rhTSH have the same performance in detecting recurrence. If this is not true, other considerations would need to be included and cost-effectiveness of rhTSH may vary.

4.4 Comparisons with published studies

There were four included studies looking at the cost-effectiveness of rhTSH compared to THW. Three studies[15, 25, 27] estimated quality of life benefits using exclusively Pacini 2006 trial[23]. Consequently, there are two major limitations in these analyses. Firstly, Pacini collected utility only twice throughout the trial: at baseline and just before ablation. This implies that all three analyses had to heavily rely on several assumptions to model quality of life changes over time. Secondly, Pacini 2006 trial[23] was found to be an outlier in the clinical

meta-analysis (see Appendix A:) as it estimated a much larger difference in quality of life between THW and rhTSH than the other two trials. As Table 4 in section 2.3.3 showed, difference in quality of life at ablation was significantly higher in Pacini and less than half in ESTIMABL[24] and HiLO trials[13]. It is not surprising, therefore, that economic evaluations exclusively based on Pacini 2006 estimated large QALYs benefits with rhTSH, which affected the overall conclusion on cost-effectiveness: Mernagh 2010[15] found a cost per QALY of £9,285, Sohn 2015 found a cost per QALY of £23,123 and Vallejo 2017[27] found rhTSH dominating THW.

This is in line with the cost per QALY of £12,950 found in this analysis when effectiveness was estimated using only the trial of Pacini 2006. By contrast, this analysis had two main advantages. Firstly, it was based on a meta-analysis of all three trials available which reduces uncertainty and biases caused by heterogeneity. Secondly, as quality of life over time was estimated using the utility curve observed in ESTIMABL by Borget 2015[6], this analysis had to rely less on assumptions than the previous analyses based on Pacini 2006 and could use a realistic and observed utility curve over time instead.

A fourth economic analysis[6] was based on ESTIMABL trial instead and was the only one finding rhTSH not cost-effective. This is in line with the results of this analysis finding lower cost-effectiveness when effectiveness was estimated using ESTIMABL or HiLo trial.

4.5 Conclusions

This economic evaluation based on a meta-analysis of all three trials comparing rhTSH and THW found rhTSH to be potentially cost-effective in England at a £30,000 threshold. This analysis was very sensitive to adherence to treatment and price of T3 in England. When lower levels of adherence in THW group were tested, rhTSH was found to be more cost effective. By contrast, when T3 was excluded from the analysis due to its unusual price, rhTSH was found to be not cost-effective at either £20,000 or £30,000 threshold.

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Appendices

Appendix A: Meta-analysis

Figure 6: SF-36 physical functioning score

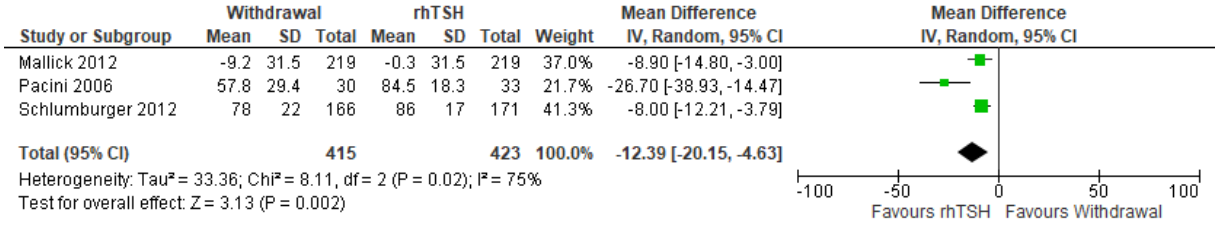

Figure 7: SF-36 social function score

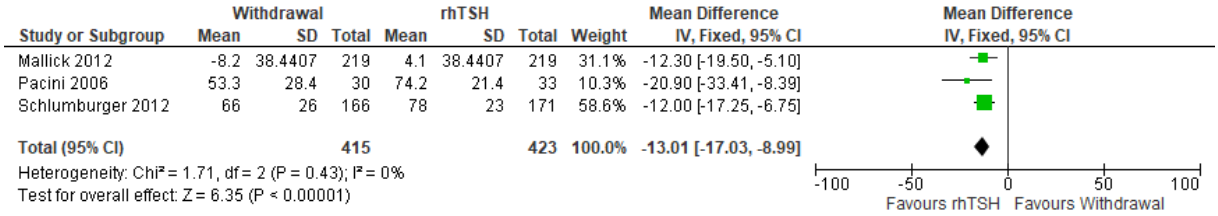

Figure 8: SF-36 role physical score

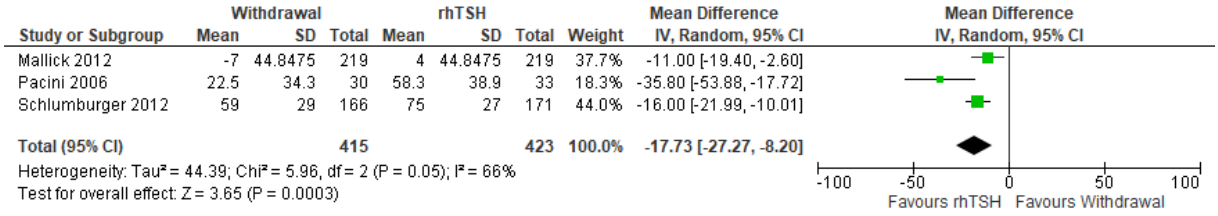

Figure 9: SF-36 role emotional score

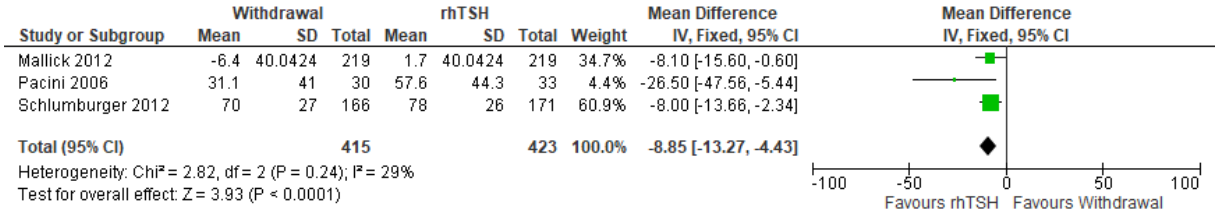

Figure 10: SF-36 mental health

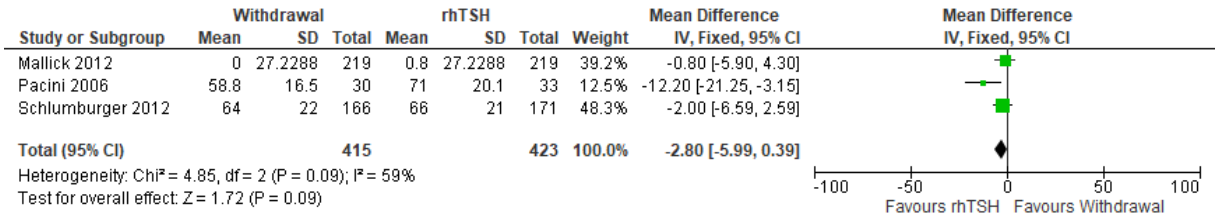

Figure 11: SF-36 vitality score

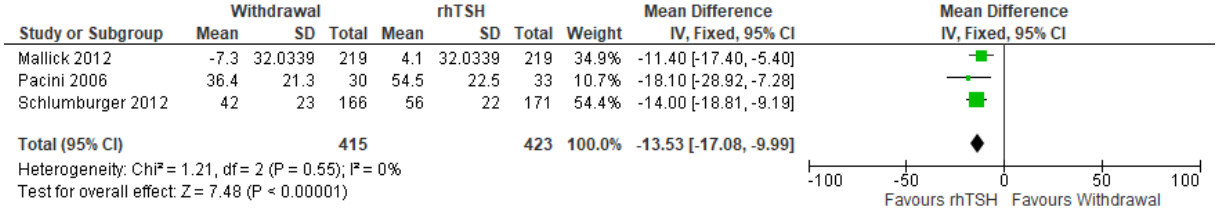

Figure 12: SF-36 body pain

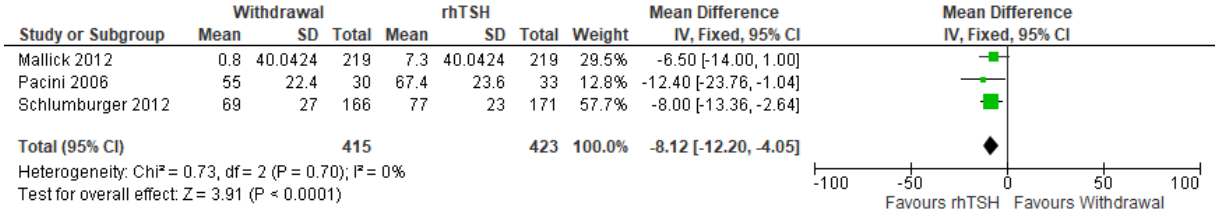

Figure 13: SF-36 general health