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Cost-effectiveness of testosterone treatment utilising individual patient data from randomised controlled trials in men with low testosterone levels

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Abstract

Background: Testosterone is safe and highly effective in men with organic hypogonadism, but worldwide testosterone prescribing has recently shifted towards middle-aged and older men, mostly with low testosterone related to age, diabetes and obesity, for whom there is less established evidence of clinical safety and benefit. The value of testosterone treatment in middle-aged and older men with low testosterone is yet to be determined. We therefore evaluated the cost-effectiveness of testosterone treatment in such men with low testosterone compared with no treatment.

Methods: A cost-utility analysis comparing testosterone with no treatment was conducted following best practices in decision modelling. A cohort Markov model incorporating relevant care pathways for individuals with hypogonadism was developed for a 10-year-time horizon. Clinical outcomes were obtained from an individual patient meta-analysis of placebo-controlled, double-blind randomised studies. Three starting age categories were defined: 40, 60 and 75 years. Cost utility (quality-adjusted life years) accrued and costs of testosterone treatment, monitoring and cardiovascular complications were compared to estimate incremental cost-effectiveness ratios and cost-effectiveness acceptability curves for selected scenarios.

Results: Ten-year excess treatment costs for testosterone compared with non-treatment ranged between £2306 and £3269 per patient. Quality-adjusted life years results depended on the instruments used to measure health utilities. Using Beck depression index-derived quality-adjusted life years data, testosterone was cost-effective (incremental cost-effectiveness ratio <£20,000) for men aged <75 years, regardless of morbidity and mortality sensitivity analyses. Testosterone was not cost-effective in men aged >75 years in models assuming increased morbidity and/or mortality.

Conclusions and future research: Our data suggest that testosterone is cost-effective in men <75 years when Beck depression index-derived quality-adjusted life years data are considered; cost-effectiveness in men >75 years is dependent on cardiovascular safety. However, more robust and longer-term cost-utility data are needed to verify our conclusion.

KEYWORDS
cost-effectiveness, economic mode, hypogonadism, technology assessment, testosterone

1 | INTRODUCTION

Testosterone is the standard treatment for male hypogonadism in whom there is no satisfactory alternative treatment or 'no treatment' option. In men with organic hypogonadism, the socio-economic consequences have been modelled in addition to the clinical features,[1] and the value of testosterone replacement is widely assumed. However, testosterone is being prescribed worldwide predominantly in middle-aged and older men, and in those with co-morbidities such as obesity and type 2 diabetes and associated non-syndromic low testosterone,[2,3] for whom studies have not established robust treatment benefits.[4] The pre-treatment clinical characteristics of these men differ from those with organic or syndromic hypogonadism in that anaemia and osteoporosis are far less prevalent. In the setting of an equivocal treatment benefit, cost-effectiveness would play a major role in defining the overall value of treatment, but there exists little data to inform the cost-effectiveness of testosterone therapy in men, which has hitherto only been investigated in men receiving testosterone undecanoate injections for Klinefelter syndrome and late-onset hypogonadism.[5]

We conducted an economic evaluation comparing testosterone therapy with non-treatment in men with non-syndromic low testosterone using the safety and efficacy data from an individual patient data (IPD) meta-analysis led by Imperial College London and the University of Aberdeen to collate data from placebo-controlled randomised trials (RCTs) of testosterone monotherapy in men with low testosterone. We have already reported clinical outcomes of this testosterone efficacy and safety (TestES) analysis,[6,7] which formed the basis of our economic modelling reported in this article. We have also analysed the dependency of our results on patient age, and confidence intervals (CIs) of morbidity and mortality during testosterone treatment, so as to broaden its usefulness for clinicians and healthcare providers.

2 | METHODS

A cost-utility analysis was conducted following best practices in decision modelling.[8] A cohort Markov (state transition) model incorporating relevant care pathways for individuals with low testosterone was informed by existing guidelines,[9,10] our IPD meta-analysis[6,7] and input from clinical investigators (Figure 1). The model was developed in TreeAge Pro (Healthcare Version).[11] The analyses adopted an National Health Service (NHS) and personal and social services perspective.[12]

2.1 | Study population, adverse event and mortality data

Inclusion and exclusion criteria for our systematic review and meta-analysis have been published.[6] In brief, our model is based on extant placebo-controlled double-blind RCTs of testosterone monotherapy in men with low testosterone (<12 nmol/L) up to 2021. Three starting age categories were defined to illustrate the age groups of clinical interest (<60 years, 60–75 years and >75 years): that is, 40-, 60- and 75-year-old men. In the absence of any guidance from existing literature, the specific age groups were selected to depict three illustrative scenarios of men having different cardiovascular risk profiles treated for low testosterone. Mortality, cardiovascular and cerebrovascular outcomes were taken from our IPD analysis[6] (Table 1). The underlying risks of experiencing a cardiovascular or cerebrovascular event were derived from the British Heart Foundation Heart and Circulatory Disease Statistics 2020[13] (Table 2). Age-specific mortality rates[14] were used to model death from all causes in men with no complications and adjusted using a standardised mortality ratio

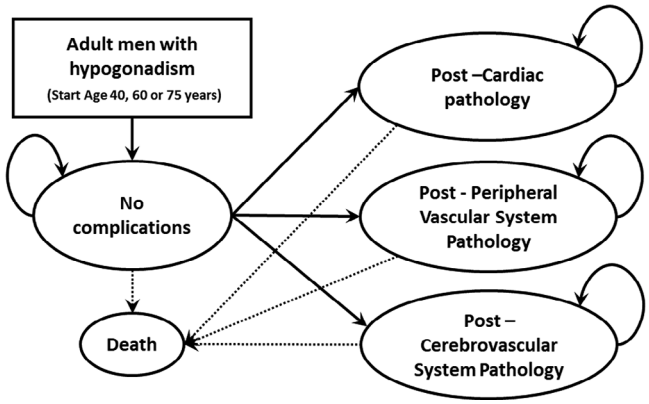

FIGURE 1 Simplified schematic of economic model structure. All individuals start at the 'No complications' health state but may move to one of three post-complication Markov states: cardiac pathology; pathology of the peripheral vascular system; pathology of the cerebrovascular system. Death is an absorbing Markov health state. Markov cycle length was defined as 1 month.

in men with complications using previously published literature[15–17] (Table 1).

2.2 | Health state utilities

We conducted a systematic review of RCTs collecting quality of life (QoL) data during testosterone treatment, revealing the use of instruments such as EQ-5D, SF-36 or SF-12, from which direct measures of utility could be obtained.[7] In addition, instruments related to sexual function, psychological function or QoL were checked against the Oxford database of mapping studies.[18] Four study datasets provided SF-36 and three provided Beck depression inventory (BDI) scores. We used the SF-36 data to estimate direct utility scores for testosterone and no treatment at 26 weeks post-randomisation. In addition, we mapped from the BDI score to the EQ-5D utility score following the methods provided by Grochtdreis et al.[19] The BDI data allowed us to estimate the utility difference between no treatment and testosterone at circa 7 months post-randomisation. Mixed effect regression models (random effects on the study and fixed effects on participants) were used to estimate the difference in utility score between testosterone and no treatment. Utility multipliers for testosterone and no treatment were calculated by dividing these utility scores by the population norm for the sample.[20] Finally, these utility multipliers were applied to the general population EQ-5D score formula proposed by Ara and Brazier to obtain the age and male-specific utility score for the 'no complications' health state for testosterone and no treatment, respectively[21](Table 3).

TABLE 2 Underlying monthly risk of cardiovascular events as per Circulatory Disease Statistics 2020, British Heart Foundation.

Variable	Point estimate	Distributional form
45–54 years	0.0005	Beta: alpha = 553; beta = 99,447
55–64 years	0.0011	Beta: alpha = 1318; beta = 98,682
65–74 years	0.0020	Beta: alpha = 2335; beta = 97,665
75+ years	0.0038	Beta: alpha = 4456; beta = 95,544

2.3 | Costs of testosterone therapy

We used published data to identify the four most prescribed testosterone formulations and annualised dosing in the UK to define the percentage of men prescribed testosterone using each formulation[22]: testosterone 16.2 mg/g gel (Testogel), 29%; testosterone 2% gel (Tostran), 15%; combined testosterone esters (Sustanon 250), 8%; testosterone undecanoate 1 g (Nebido), 46%. British National Formulary and the NHS indicative prices were used to value these medicines (Table 4). Resource use as treatment initiated with medication, administration (when applicable) and monitoring were included, based on an information sheet for Primary Care prescribers for testosterone for adult males with hypogonadism from the Nottinghamshire Area Prescribing Committee.[23] Testosterone level, prostate-specific antigen (PSA), haemoglobin (Hb) and haematocrit, liver function test (LFT) and lipid profile were assumed for all products at baseline and annually thereafter. In addition, testosterone levels at 4–6 weeks for gel-administered products only and at 3–6 months for gel products and Sustanon were considered. Concurrent with the third dose of Nebido (4 months) testosterone level, PSA, Hb and haematocrit, LFT and lipid

TABLE 1 Individual patient data meta-analysis outcomes incorporated into the economic model and underlying mortality risks of cardiovascular events.

Variable	Point estimate	RR 95% CI	Distributional form	Source
Relative risk for any cause mortality	0.47	(0.18, 1.25)	LogNormal	Hudson et al.[6]
Relative risk of cardiovascular and/or cerebrovascular complications	1.06	(0.82, 1.38)	LogNormal	Hudson et al.[6]
Cardiac pathology	2			Smolina et al.[15]
Cerebrovascular system pathology				Bronnum-Hansen et al.[17]
First year	4.73			
Subsequent years	2.32			
Peripheral vascular system pathology	3.14			Criqui et al.[16]

Abbreviations: CI, confidence interval; RR, relative risk.

TABLE 3 Utility scores for the *no complication* health state for *testosterone* and *no treatment*.

Testosterone	Coefficient	SE	95% CI	Distributional form
SF-6D	0.0042	0.0084	(−0.012 to 0.021)	Normal
Mapped EQ-5D	0.0295	0.0087	(0.013 to 0.046)	Normal
	Testosterone	**No treatment**		
SF-6D-based utility scores				
40 years old	0.910	0.905		
60 years old	0.838	0.834		
75 years old	0.767	0.763		
BDI-based utility scores				
40 years old	0.854	0.823		
60 years old	0.787	0.758		
75 years old	0.720	0.693		

Abbreviations: BDI, Beck depression inventory; CI, confidence interval; SE, standard error.

profile were assumed. The unit cost for these tests was obtained from the National Schedule of NHS Costs 2019—2020 (Table 4). Phlebotomy cost was added to the cost of the tests. In the absence of published data on the split of treatment settings providing testosterone treatment worldwide, we assumed that half of the patients were monitored in the hospital and half in the community, with an equal share of hospital visits between the Endocrinology and Urology services. A 63% reduction in erectile dysfunction medications was assumed for individuals during testosterone therapy.[24] The cost of phosphodiesterase-5 inhibitors (PDE5i) was calculated accordingly.

2.4 | Healthcare costs of no treatment

As the main symptom of hypogonadism is reduced sexual function, 96% of the cohort was assumed to use PDE5i for erectile dysfunction with one annual primary care visit.[25] Published data were used to allocate, proportionately, the associated monthly cost for sildenafil (£1.27 for four tablets—one per week) and tadalafil (£4.66 for 28 tablets—one per day).[26,27]

2.5 | Health state utilities and costs associated with complications

The unit cost and utilities associated with cardiovascular, cerebrovascular and peripheral vascular system events were sourced through searches of technology appraisals, clinical guidelines and health technology assessments on the National Institute for Health and Care Excellence (NICE) and the National Institute for Health and Care Research (NIHR) websites. These sources were favoured as they are based on comprehensive literature reviews related to the condition of interest, utilise large datasets of UK patients and have been used in the NHS decision-making process. Following the method used in NICE Clinical Guidelines (CG181), each complication was attributed a short and long-term cost and utility multiplier.[28] Hence, patients accrue alternative costs and utilities for each condition in the short and long-term depending on whether it can be considered an ongoing or immediate health event (Tables S1 and S2).[28–37]

2.6 | Model validation

Several steps were taken to guarantee the quality of the model.[38] The model structure was agreed upon with the members of the Advisory Group for this project (three clinicians, two statisticians, one health economist and one patient) to secure the model structure's face validity. Model formulae were verified using an external software and model behaviour was extensively tested assuming alternative model input values. Finally, Markov traces were extracted and cumulative proportions at 10 years were compared against results from external risk prediction tools.[39]

2.7 | Time horizon and discounting

We considered a 10-year time horizon. Given the 3-year follow-up of the RCTs included in the synthesis of clinical effectiveness evidence, the extrapolation of clinical effects from the IPD analysis beyond 10 years would be highly uncertain. However, we have also considered a lifetime time horizon within the sensitivity analysis.[40] A half-cycle correction was applied and future costs and quality-adjusted life years (QALYs were discounted at a rate of 3.5% per annum.[40]

2.8 | Model analysis

The analysis captures the cumulative health and social care costs from the perspective of the NHS and QALYs accrued by patients receiving testosterone or no treatment. The model was run probabilistically

TABLE 4 Unit cost for testosterone replacement and follow-up.

Product/service	Price	Notes/assumptions
Testosterone products		
Testogel 16.2 mg/g gel (Besins Healthcare [UK] Ltd.)	£31.11	One pump actuation delivers 1.25 g of gel containing 20.25 mg of testosterone (SmPC) Two pumps per day with each prescription lasting 5 weeks
Tostran 2% gel (Kyowa Kirin Ltd.)	£28.63	One press of the canister piston delivers 0.5 g of gel containing 10 mg testosterone (SmPC) Four press deliver the daily needed doses with each prescription lasting 4 weeks
Sustanon 250 mg/1 mL solution for injection ampoules (Aspen Pharma Trading Ltd.)	£2.45	Each ampoule contains 1 mL arachis oil containing the active substances 12 injections in a year (Channa, personal communication, 25/5/2020). 50% of patients would self-administer and 50% delivered by a nurse[a]
Nebido 1000 mg/4 mL solution for injection vials (Bayer Plc)	£87.11	Each mL solution for injection contains 250 mg testosterone undecanoate corresponding to 157.9 mg testosterone. Each ampoule/vial with 4 mL solution for injection contains 1000 mg testosterone undecanoate corresponding to 631.5 mg testosterone (SmPC) Loading phase: first injection, then 6 weeks, and then every 12 weeks (medicines.org.uk)
Tests		
Testosterone level	£1.22	National schedule of NHS costs 2019–2020; Directly Accessed Pathology Services, DAPS04
PSA (+digital rectal examination if clinically indicated) in men >40 years	£1.22	National schedule of NHS costs 2019–2020; Directly Accessed Pathology Services, DAPS05
Hb and haematocrit	£2.58	National schedule of NHS costs 2019–2020; Directly Accessed Pathology Services, DAPS05
LFT	£1.22	National schedule of NHS costs 2019–2020; Directly Accessed Pathology Services, DAPS04
Lipid profile	£1.22	National schedule of NHS costs 2019–2020; Directly Accessed Pathology Services, DAPS05
Phlebotomy	£4.77	National schedule of NHS costs 2019–2020; Directly Accessed Pathology Services, DAPS08
Monitoring visits		
GP visit	£39	GP—per surgery consultation lasting 9.22 min. PSSRU—Unit Costs of Health and Social Care 2020
Hospital visit—urology	£111	Total for service code 101. National schedule of NHS costs year: 2019–2020—all NHS trusts and NHS foundation trusts—outpatient attendances data
Hospital visit—endocrinology	£162	Total for service code 302. National schedule of NHS costs year: 2019–2020—all NHS trusts and NHS foundation trusts—outpatient attendances data

Abbreviations: GP, general practitioner; Hb, haemoglobin; LFT, liver function test; PSA, prostate-specific antigen; PSSRU, Personal Social Services Research Unit; SmPC, summary of product characteristics.

[a]The cost of testosterone injection administration assumed 15 min of a nurse at a cost of £11.38 (i.e., 50% hospital nurse Band 6 at £49 per hour and 50% GP nurse at £42 per hour).

(10,000 Monte Carlo simulations) to show the influence of the joint uncertainty in the modelled outputs (cost and QALYs) arising from the uncertainty in the input parameters. Beta, gamma and lognormal distributions were attached to probabilities, costs and relative effects parameter values, respectively, and normal distributions to testosterone utility difference (estimated from the regression analysis of the TestES data) and the utility multipliers attached to complications. Incremental cost-effectiveness ratios (ICER) were estimated to compare testosterone against no treatment. The ICER is defined as the ratio of the difference in expected costs over the difference in expected QALYs between testosterone and no treatment. Cost and QALYs were averaged across the 10,000 iterations, with the ICER calculated as the average difference in costs and QALYs between testosterone and no treatment.

Results are reported for four scenarios defined according to alternative assumptions around key model effectiveness parameter for

TABLE 5 Incremental cost-effectiveness ratios (ICERs) for selected ad hoc scenarios.

	Relative risk of complications			
Relative risk of all-cause mortality	**0.82**	**1**	**1.06**	**1.38**
40-Year-old cohort starting age				
0.18	9981	10,436	10,592	11,469
0.47	10,579	11,077	11,249	12,214
1	11,885	12,485	12,692	13,865
1.25	12,624	13,283	13,512	14,813
60-Year-old cohort starting age				
0.18	6235	6895	7127	8479
0.47	7423	8282	8587	10,405
1	11,561	13,303	13,948	18,105
1.25	15,838	18,825	19,982	28,169
75-Year-old cohort starting age				
0.18	2897	3463	3668	4920
0.47	3720	4573	4890	6949
1	9485	13,935	16,033	43,742
1.25	64,612	−131,813	−71,565	−24,595

Note: Negative ICERs mean no treatment less costly and more effective than testosterone.

testosterone versus no treatment: the relative risk (RR) of mortality, the RR of cardiovascular, peripheral vascular and cerebrovascular complications, and the utility difference between testosterone and no treatment. These results are reported for three age groups: 40-, 60- and 75-year-old, and by the alternative sources used to calculate the utility multipliers (i.e., SF-36 based or BDI mapping). Further, ICERs are also reported for further ad hoc scenarios where the upper and lower 95% CI limits for the RR of all-cause mortality and complications were used as mean input estimates together with BDI-based utilities. All these effects were sustained for the 10-year time horizon.

3 | RESULTS

Expected costs were predictably higher for testosterone versus no treatment, reflecting the costs of the therapy and associated follow-up (Table S3). Costs also increased with age because of the higher chance of experiencing a complication and in scenarios with higher risks of complications (Table S3). QALYs decreased in older men because of age and a higher rate of complications.

With EQ-5D utility scores mapped using BDI multipliers and mortality and cardiovascular complication RRs of 0.46 and 1.06, respectively, all ICERs were below the £20,000 cost-effectiveness threshold applied in the UK[40] (Table 5). ICERs for further ad hoc scenarios using EQ-5D utilities calculated with BDI multipliers are reported in Table 5. Scenarios were selected for three age groups using mortality and morbidity RRs and their 95% CIs from our meta-analysis. As expected, ICER for the scenarios where testosterone is protective (e.g., RR of mortality = 0.18; RR of complications = 0.82) was lower than those scenarios where testosterone is not protective (e.g., RR of mortality = 1.25; RR of complications = 1.38). Moreover, given the relatively low risk of all-cause mortality for 40- and 60-year-old, the ICERs remained within the UK cost-effectiveness threshold[40] of £20,000 per QALY gained for all but one scenario (green text in Table 5); an all-cause mortality RR above 1 increased the ICER beyond the £20,000 threshold for the 75-year-old cohort (red text in Table 5).

QALYs and incremental QALYs varied according to the instrument used to measure health state utilities. Detailed analyses including cost, incremental cost, comparison of QALYs, incremental QALYs, ICER and probability of testosterone cost-effectiveness with two different health-utility measures are included in Table S3. When SF-6D multipliers were used, the majority of the ICERs were well above the usual UK cost-effectiveness threshold[40] for decision making, with all scenarios showing a low probability of testosterone being cost-effective. The exceptions to this were scenarios where an all-cause mortality RR of 0.46 was assumed for the 60-year-old cohorts (ICER = £19,444; probability cost-effective = 0.55) and 75-year-old cohorts (ICER = £6778; probability cost-effective = 0.87).

Finally, when no difference in mortality or QoL was assumed together with an increased risk of complication from testosterone, 'no treatment' would dominate testosterone; this is, 'no treatment' is expected to generate lower costs and higher QALYs compared with testosterone (last row for each age group in Table S3).

3.1 | Cost-effectiveness acceptability curves

The cost-effectiveness acceptability curves (CEAC) for testosterone for selected scenarios for the 40-, 60- and 75-year-old starting age

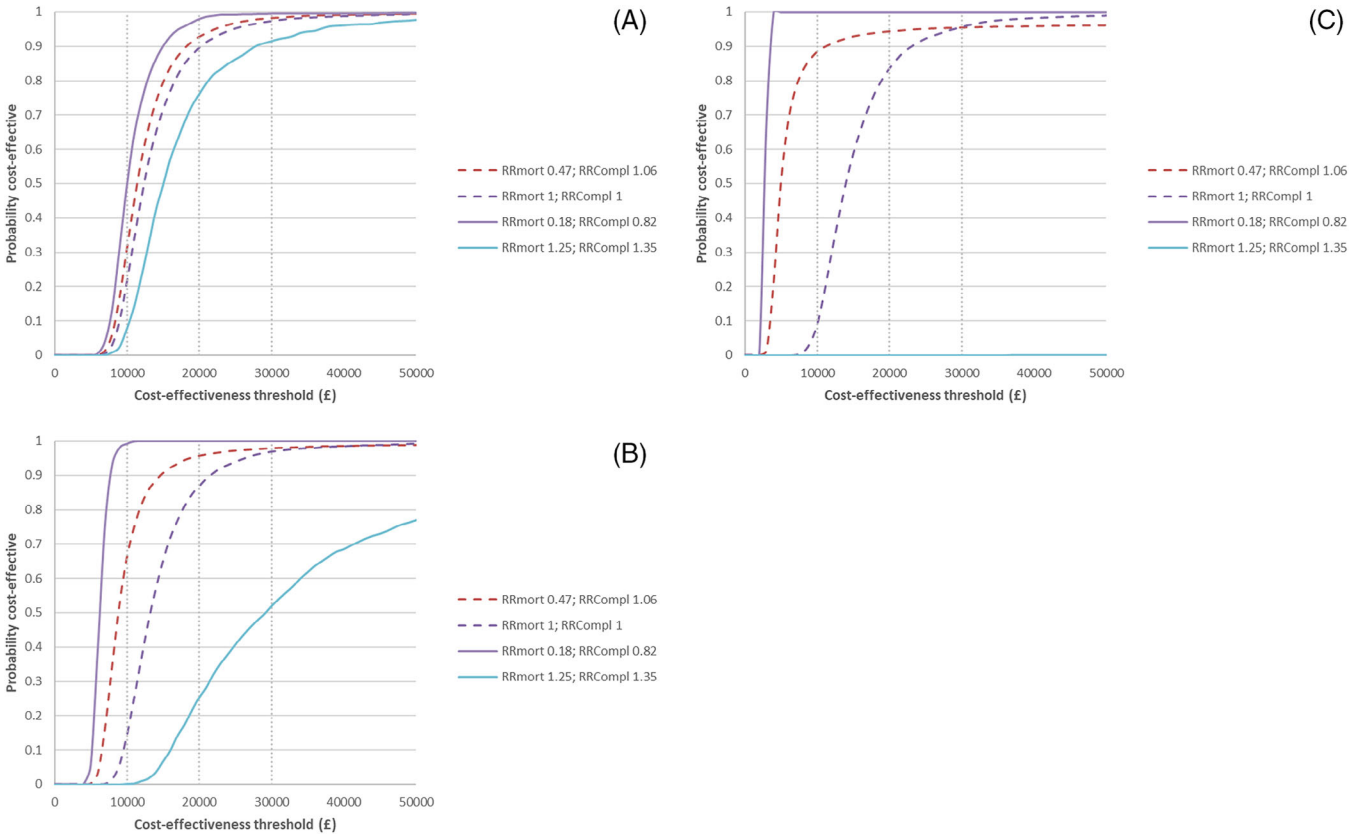

FIGURE 2 Cost-effectiveness acceptability curves for testosterone: alternative scenarios. The cost-effectiveness acceptability curves (CEAC) for testosterone for selected scenarios for the 40-year-old (A), 60-year-old (B), and 75-year-old (C) starting age cohorts are reported. These are developed for the Beck depression inventory (BDI)-multiplier-based utilities and maintained for the 10-year time horizon. RRCompl, relative risk of complications; RRmort, relative risk of mortality.

cohorts are reported in Figure 2. The CEACs show the probability of testosterone being cost-effective for a range of cost-effectiveness threshold values and illustrate the decision uncertainty because of second-order uncertainties around the model input parameter values. These are reported for the BDI-multiplier-based utilities (more favourable for testosterone) and maintained for the 10-year time horizon. The CEACs show that the probability of testosterone being cost-effective rises as the cost-effectiveness threshold increases. In addition, the CEACs confirm that the probability of testosterone being cost-effective depends on the RRs for all-cause mortality and complications, impacting more on the 60- and 75-year-old cohorts where the baseline risk is higher. As an illustration, the probability of testosterone being cost-effective at a £20,000 cost-effectiveness threshold and RR mortality of 1.25 and RR complications of 1.38 falls by 76%–25% and 0% for the 40-, 60- and 75-year-old starting age cohorts, respectively (Figure 2, light blue line).

4 | DISCUSSION

We have conducted the first cost evaluation for testosterone treatment in middle-aged and older men with low testosterone. When the BDI-based utility scores were used, our results suggest testosterone was cost-effective irrespective of the morbidity and mortality sensitivity analyses in men below 75 years.

Our analysis is strengthened by its derivation from a large IPD dataset, from which clinical effectiveness, safety and health utility were extracted for men with low testosterone comparing testosterone with no testosterone treatment. Similarly, reporting multiple ad hoc scenarios based on 95% CIs for RRs of mortality and complications would provide the opportunity to utilise these data in the context of emerging safety data on testosterone treatment in this population. These scenarios are illustrative of a range of patient and healthcare provider characteristics; however, not limited to what we have reported in the results. Model can be modified based on the healthcare setting, for example, depending on treatment and monitoring regimes used and contribution of community and hospital towards patient care.

There are also limitations to our analysis. We have assumed no discontinuation of treatment for those individuals receiving testosterone. The implication of this structural assumption is that all the individuals under the testosterone strategy will accrue the cost and benefits of testosterone in the long term. A small proportion of hypogonadal men might discontinue testosterone during the first year of treatment with most of them resuming treatment after a short period of time.[41] While the assumption of no discontinuation constitutes a limitation

of our model, allowing for the cost of testosterone and limited QoL benefits seems to be supported by the long-term QoL IPD analysis results where no differences in utilities were observed. A limitation of the mapping approach provided by Grochtdreis et al. is that it was mapped within the psychotherapeutic outpatient setting, which may not be generalisable to our population.[19] Furthermore, the predictive performance of authors' model in the validation samples was better for individuals with good health than for individuals with bad health. This is an indication of a systematic bias in the estimation of the mapped EQ-5D utility scores with unknown implications for the cost-effectiveness of testosterone.[42] This systematic bias is a source of uncertainty that could not be evaluated through sensitivity analysis. It is worth noting that the RR for mortality was based on a small number of events[6]; as such the results for the scenarios where a reduced risk of mortality for testosterone was considered should be taken with caution. Moreover, the estimate for the RR of complications was based on events in 120 individuals out of 1601 (7.5%) and 110 individuals out of 1519 (7.2%) for the testosterone and placebo groups, respectively.[6] However, the best estimate was applied in the economic model in the context of a probabilistic analysis that appropriately characterised the uncertainty around the point estimate. Alternative treatment options including lifestyle modifications[43] and PDE5i[44] can potentially be used for some of these men and our analysis has not compared the cost-effectiveness of testosterone treatment with these treatment modalities. These would be considered in selected men with low testosterone. Our analysis is based on data from RCTs while the cost-effectiveness can vary in the real world because of more diverse patient population, less stringent patient follow-up and variable patient adherence.

To our knowledge, there is only one previous economic evaluation of testosterone treatment in men with low testosterone, which was limited to testosterone undecanoate injections in men with Klinefelter syndrome and late-onset hypogonadism, in Sweden.[5] The authors concluded that lifelong testosterone was cost-effective in these patients. Our results are comparable to those reported in the Swedish study when the BDI-based utilities were used.

Our analysis underlines that all-cause mortality is a strong driver for the value of testosterone, particularly for older men. This is because of the higher underlying mortality risk of these populations compared with that of the 40-year-old cohort. Additionally, the higher incremental cost of testosterone treatment in older men seen in our study requires consideration within healthcare budgets. Similar cardiovascular events between testosterone and placebo in the recently published TRAVERSE randomised placebo-controlled study would strengthen the cost-effectiveness of treatment based on our ad hoc scenarios.[45] However, both the TRAVERSE study and our IPD meta-analysis show only short-to-medium-term safety data, with long-term safety yet to be studied. The safety and efficacy of testosterone in older men with low testosterone and co-morbidities are beyond the scope of this economic evaluation. Therefore, the economic value of testosterone treatment in these men revealed in this study should not be directly equated to clinical appropriateness for treatment.

The cost-effectiveness of testosterone was much greater when BDI-based utilities were applied than with SF-6D utilities. This difference was most pronounced in men aged 40–60 years, highlighting the relevance of sexual symptoms to the value of treatment. The BDI evaluates key symptoms of depression such as mood, pessimism, sense of failure, self-dissatisfaction, guilt, self-dislike, self-accusation, social withdrawal and loss of libido.[46] In contrast, the SF-6D is a generic preference-based measure of health-related QoL based on the SF-36. The algorithm uses responses to 11 of the 36 items included in the SF-36 to generate utility scores.[47] This sub-set of questions covers a range of dimensions such as physical functioning, physical role, emotional role, pain, mental health and how physical and emotional problems might have interfered with the respondent's social activities. The changes in QoL from testosterone might act through particular dimensions in individuals with hypogonadism that are not covered by these dimensions. Furthermore, more robust mapping of health utilities using the EQ-5D questionnaire would enable a more precise estimation of the value of testosterone treatment in men.

5 | CONCLUSIONS

Our analysis suggests that testosterone treatment is cost-effective in middle-aged men when health-utility benefits are assumed. Testosterone may also be cost-effective in older men with non-syndromic low testosterone, but this is contingent on its cardiovascular safety. More robust data on health utilities and longer-term safety data are needed to verify our conclusions.

AUTHOR CONTRIBUTIONS

Channa N. Jayasena conceived the study. Rodolfo Hernández, Jemma Hudson, Moira Cruickshank, Siladitya Bhattacharya, Miriam Brazzelli and Channa N. Jayasena designed the study. Rodolfo Hernández, Paul Manson, Siladitya Bhattacharya and Miriam Brazzelli performed the cost analysis. Richard Quinton, Waljit S. Dhillo and Channa N. Jayasena incorporated the clinical interpretation into the analysis. All authors revised and edited the manuscript. Rodolfo Hernández and Nipun Lakshitha de Silva wrote the initial manuscript. All the other authors revised the manuscript. All authors reviewed and confirmed the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Siladitya Bhattacharya received Royalties from Cambridge University Press for book, honorarium for lectures from Merck, Organon, Ferring, Obstetric and Gynaecological Society of Singapore and Taiwanese Society for Reproductive Medicine, Support from Merck, ESHRE and Ferring for attending meetings as speaker and participated in METAFOR and CAPE Trials Data Monitoring Committees. The remaining authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supporting information of this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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