**Title:** Adjuvant Statin Therapy for Esophageal Adenocarcinoma: a cost-utility analysis

**Authors:** Rebekah Fong Soe Khioe, M.S.[1], Chris Skedgel, Ph.D.[1], Andrew Hart[1,2], Mike Lewis[2], Leo Alexandre[1,2]

**Authors' affiliations and addresses:** [1] Norwich Medical School, Bob Champion Research and Education Building, James Watson Road, University of East Anglia, Norwich Research Park, NR4 7UQ, UK.

[2] Department of Gastroenterology, Norfolk & Norwich University Hospital, Colney Lane, Norwich, NR4 7UY, UK.

**Authors' Email:**

Rebekah Fong Soe Khioe, MSc: R.Fong-Soe-Khioe@uea.ac.uk

Chris Skedgel, PhD: C.Skedgel@uea.ac.uk

Andrew Hart, FRCP, MD: A.Hart@uea.ac.uk

Mike Lewis FRCS, MD: michael.lewis@nnuh.nhs.uk

Leo Alexandre, MRCP: Leo.Alexandre@uea.ac.uk

**Corresponding Author:**

Rebekah Fong Soe Khioe

R.Fong-Soe-Khioe@uea.ac.uk, 01603 593942

**Author contributions:** R.FSK, C.S, L.A, A.H and M.L contributed to the writing and revisions of the final manuscript. C.S. designed model with R.FSK contributing to the collection and analysis of data.

**Conflicts of Interest:** R.FSK, C.S, L.A, A.H and M.L have no conflicts of interest to declare.

**ABSTRACT**

**Background**

Emerging preclinical evidence indicates statins, medications commonly used in the prevention of cardiovascular disease, inhibit proliferation, promote apoptosis and limit invasiveness of esophageal adenocarcinoma (EAC). Population-based observational data demonstrates statin treatment after diagnosis of EAC is associated with significant reductions in all-cause and cancer-specific mortality. A feasibility study of adjuvant statin therapy following potentially curative resection for EAC has completed, with planned progression to a full phase III randomised controlled trial

**Aim**

To estimate the cost-utility of statin therapy following surgical resection for EAC from an NHS perspective.

**Methods**

A Markov model was developed to estimate the costs and outcomes (quality adjusted life years, QALYs) for hypothetical cohorts of patients with EAC exposed or not exposed to statins following potentially curative surgical resection. Model parameters were based on estimates from published observational and trial data. Costs, utilities and transition probabilities were modelled to reflect clinical practice from a payer's perspective. Probabilistic and one-way sensitivity analyses were performed to account for uncertainty in key parameters.

**Results**

Overall, a cost-saving of £6,781 per patient was realised with statin treatment compared to no statins. In probabilistic sensitivity analysis, 99% of all iterations were

cost-saving and  99% of all iterations were less than £20,000 per QALY gained. These results were robust to changes in the price and effectiveness of statins..

**Conclusions**

The cohort exposed to statins had lower costs and better QALY outcomes than the no statin cohort. Assuming a causal relationship between statin exposure and outcomes suggests that statins following resection of EAC is a cost-saving treatment.

**Key Words:** HMG-CoA; cost-effectiveness; esophageal cancer.

**Key Points for Decision Makers:**

- Epidemiological and trial data can be efficiently applied and drawn together within modelling studies to estimate the associated economic impact of treatments upon UK NHS resources (i.e. the cost per quality-adjusted life-year (QALY)).
- Assuming a causal improvement in survival post-resection of esophageal adenocarcinoma (EAC), statin therapy is very likely to be a cost-effective treatment strategy
- The development of randomised controlled trials to establish the efficacy of statins as an adjuvant treatment for EAC are warranted from a clinical perspective.

## 1. INTRODUCTION

Esophageal cancer (EC) is the 8th most common cancer worldwide and is associated with a dismal prognosis[1]. In the United Kingdom (UK) there were 8,784 newly registered cases in 2013 and 7,701 deaths, ranking EC as the 4th and 6th cause of cancer death in men and women respectively in 2014[2]. Within the western world esophageal adenocarcinoma (EAC) is the commonest histological subtype of esophageal malignancy[3]. Since the 1970s the incidence of EAC has risen six-fold in England and Scotland, with the UK currently having the highest age-standardised incidence rate in the western world[4], [5]. In 2012-13 the cost of esophageal cancer was estimated at £134 million, approximately 0.3% of total NHS costs and as the incidence continues to rise, the economic burden to National Health Service (NHS) resources will increase[6].

The mainstay of treatment in patients with potentially curable EAC is surgery with or without chemotherapy or chemo-radiotherapy[1]. Most recent trial data show that patients with esophageal and junctional adenocarcinomas treated with pre-operative chemo-radiotherapy have a five-year survival of 45%, at best[7], with most deaths attributable to recurrent disease.

There is currently a substantial research focus on the anti-cancer effects of statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors), medications commonly prescribed for the prevention of primary and secondary cardiovascular disease[8]. There is growing experimental evidence to suggest statins promote apoptosis, inhibit proliferation and limit invasiveness in EAC cell lines[9]–[12]. There is strong epidemiological evidence for statins reducing the risk of cancer-related mortality. The most recent systematic review and meta-analysis of

observational studies included 95 cohorts with over 1.1 million cancer patients (from multiple sites) demonstrated post-diagnosis statin use was associated with a significant reduction in all-cause mortality (HR 0.65, 95% CI 0.60 – 0.72), with similar effect sizes for both cancer-specific mortality and disease-free survival[13]. A population-based cohort study of 4445 patients with esophageal cancer conducted in the UK with linkage between the Clinical Practice Research Datalink (CPRD), (a large primary care database of anonymised medical records of over 11.3 million patients from over 560 UK general practices), National Cancer Data Repository, and Office for National Statistics Datasets similarly demonstrated significant reductions in EC-specific mortality (HR 0.63 95% CI 0.38 - 0.96) and all-cause mortality (HR 0.63 95% CI 0.43 - 0.92) associated with statin use following diagnosis of EAC[14]. Statin use was modelled as a time-dependent exposure, adjusted for age, gender, body mass index, smoking status, cardiovascular disease, diabetes mellitus, surgery, chemotherapy, radiotherapy and medication use (aspirin, angiotensin-converting enzyme inhibitors, and angiotensin 2-receptor blockers, beta-blockers and nonsteroidal anti-inflammatory drugs). Based on the emerging experimental and observational data, the STAT-ROC feasibility study[15] has been completed to determine the prospect of investigating adjuvant statin therapy in the setting of prevention of recurrence of potentially curative EAC. The feasibility study was a multi-centre, double-blind, parallel group, randomised trial to estimate the recruitment, retention, drug adherence, and safety of statins, which strongly supports the feasibility of a future phase III randomised-controlled trial, which is currently in development.

In deciding patient care to the individual, delivery of service is influenced by the impact of care upon the individual's survival and quality of life. Additionally, the cost

burden to the NHS is likely to affect the choice of treatment recommended by decision-makers. The National Institute for Health and Care Excellence (NICE) clinical guideline CG181 recommend[8] patients are treated with statins, for primary and secondary prevention of cardiovascular disease at the NICE threshold value of £20,000 cost per QALY gained, but the 'value for money' of statins as an adjuvant treatment for EAC recurrence following potentially curative surgery is unknown.

In light of the economic burden upon NHS resources and emerging experimental and observational data surrounding statin treatment for patients post-diagnosis of EAC, we evaluated the cost-effectiveness of statin therapy following potentially curative resection (esophagectomy) for locally advanced EAC. Current UK practice, as reflected in a recent national audit is either surgery alone or in combination with peri-operative chemotherapy [used in > 80%][16]. We modelled, integrating observational and trial data, the potential for statin therapy to be cost-effective in terms of a cost per quality-adjusted life year (QALY) gained. The aim of this study was to determine the cost-effectiveness of statin therapy as an adjuvant treatment for EAC.

## 2. METHODS

A probabilistic state-transition model was developed in Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, United States of America) to estimate the cumulative cost and QALY outcomes associated with exposure to statin use alongside standard care (surgery +/- perioperative chemotherapy) versus no statin use with standard care only, in patients following surgical resection post-diagnosis of EAC. A UK NHS payer perspective was adopted, and following NICE methods guide, costs and outcomes were discounted at 3.5% [17].

## 2.1. Model Structure

The state-transition model consisted of three possible health states by which patients progressed through. All patients began in the disease-free survival (DFS) state, following curative resection for EAC, and could transition to EAC recurrence and subsequently death by EAC or due to other causes (background mortality). Patients were also able to transition from DFS to death due to other causes, without transitioning to EAC recurrence. At entry into the model, patients in the statin arm were assumed statin users once daily and were at risk of statin-specific adverse events (AEs) within each health state. Patients in the non-statin arm received standard care only.

The model had a one-year cycle length and a lifetime horizon (30 years, reflecting life expectancy in this population). A half-cycle correction was applied to the first cycle. Figure 1 presents the model structure.

## 2.2. Transition probabilities and key model assumptions

The baseline population was modelled to reflect the demographic characteristics of patients identified in the CPRD with a diagnosis of incident esophageal or esophagogastric junction cancers. The cohort from the CPRD were 71 years old and 69% were male, which was assumed as the baseline population within the model. To model the clinical efficacy, the baseline patient population were modelled to reflect data from the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) randomised controlled trial (RCT). Briefly, the trial recruited 503 patients, predominately from the UK and Netherlands, to compare peri-operative chemotherapy to no chemotherapy in patients with resectable gastro-oesophageal adenocarcinoma. This trial was selected since the active arm largely reflects current UK practice: most patients (>80%) treated with curative intent for EAC in the UK

receive peri-operative chemotherapy. A parametric function was fitted to the disease-free survival (DFS) curve observed in the peri-operative chemotherapy arm to inform the baseline DFS in the model[18]. A Weibull distribution had the best fit to the observed data by the Kolmogorov-Smirnov statistic and Aikake's Information Criterion[19]–[21] and is illustrated in Figure 2. All patients were assumed eligible for statin therapy when they entered the model at baseline. The effect size for the association between post-diagnostic statin use and all-cause mortality from UK observation data (HR 0.63, 95% CI: 0.43;0.92) was assumed to approximate the effect size of statin use on DFS in the model[14]. Median adherence to statin therapy in the intended patient population from feasibility data is 91.5%[15]. To be conservative, in a sensitivity analysis we assumed adherence to statins was 90%.The DFS benefit of statins was assumed to persist for as long as patients continued on treatment until recurrence or death. Reflecting clinical outcomes observed in the MAGIC trial[18], patients in both arms of the model were assumed to be at risk of EAC recurrence for 6 years following successful resection with no recurrences beyond 6 years. Patients who were non-statin users or withdrew from statin therapy due to an adverse event had the same risk of progression as patients in the no treatment arm. i.e. baseline DFS.

The risk of adverse events as a result of statin use were modelled based on current clinical practice and literature[22], [23]. Where an adverse event attributed to statins occurred patients were assumed to discontinue the drug. Finegold et al.[23] report patients allocated to statin treatment versus placebo, ashaving a statistically significantly higher risk of transaminitis (elevated transaminases alanine transaminase (ALT) and/or aspartate transaminase (AST) to greater than three times

the upper limit normal (ULN)[22]) and type 2 Diabetes Mellitus (T2DM). The increased relative risk of transaminitis and of T2DM, due to statins were reported as 31.5% and 24.7%, given an average follow-up of 3.19 years[23]. The rate of new incident cases were adjusted for the follow-up period reported and were assumed to persist over the lifetime patients remained in the model. Patients experiencing transaminitis were assumed to discontinue statins and reverted to the baseline risks of disease progression, whilst patients developing diabetes continued treatment.

Allocation to statins are associated with large relative but low absolute risk of rhabdomyolysis (a severe form of myopathy characterised by muscle breakdown with myoglobin released into the systemic circulation)[22], [24]. Whilst statin-associated rhabdomyolysis events are rare, clinically, they are important as they would be expected to lead to discontinuation of treatment and in severe cases, acute renal failure and death[25]–[27]. Given these potentially severe consequences, the risk of rhabdomyolysis was included in the model to take a conservative approach in considering the costs and outcomes of statin treatment. Furthermore, to assume a simplistic model approach, the effectiveness of statins in the primary and secondary prevention of cardiovascular disease[24], [28], [29] were not included in the model, to focus wholly on the benefits in the context of esophageal cancer. Patients were also subject to an age-sex specific risk of all-cause mortality (ACM) derived from UK national life tables[30]. Assuming a predicted mortality of 8.51 per 100,000[31], ACM was adjusted for potential double counting of EAC mortality. The parameter values used within the model are shown in Table 1.

## 2.3.    Costs

The costs of statin use against no treatment were modelled with reference to the effect size demonstrated in Alexandre et al's[14] population-based data from the

perspective of the UK NHS healthcare system. All costs were inflated to 2016 prices using the Personal Social Services Research Unit (PSSRU) UK[32] hospital and community health services index. Where available, unit costs were drawn from the British National Formulary 71[33], NHS reference costs 2014/15[34] and NICE Technology Assessment (TA) costing reports[35].

The annual cost of statin treatment was calculated based on the price of a 28-day supply of each of the five statins (Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin and Fluvastatin) weighted by the proportions of patients using each formulation and multiplied to an annual cost (£2.62 x 365/28 = £34.15/year)[33]. In a sensitivity analysis we tested using the single highest monthly price in place of the weighted average price (Rosuvastatin; £29.60/month, £387.03/year).

It was assumed that patients in a disease-free state following surgery would have follow-up clinic appointments with an upper gastrointestinal (GI) surgeon every 6 months in the first two years and then yearly in the following three to five years. The cost of an EAC recurrence was estimated from NHS Reference Costs 2014/15 [34](HRG code in brackets) and included one multidisciplinary team meeting (CMDT_C), appropriate investigations; CT scan (RD20A), endoscopy (FZ57Z) and X-ray (DAPF) and any recommended oncology treatment or best supportive care. Oncology treatment costs following a recurrence were estimated assuming 25% of patients received treatment with chemotherapy, 30% radiotherapy, 1% chemoradiotherapy, and 10% stent[36]. The remaining 34% were assumed to receive treatment only with best supportive care. Median survival following recurrence was assumed to be 4 months, based upon the clinical experience of an upper GI surgeon (M.L), and was assumed to be the same in the both groups. Costs at death were based on estimates from a Marie Curie, national primary care audit of

end of life care. Hospital inpatient and community care, were estimated as £425 and £145 per day, and patients were assumed to have a median survival of 120 days (17 days as inpatient hospital care and 103 days as community care)[37].

The annual cost of type 2 diabetes mellitus was drawn from a study by Hex et al.[38]. This study was identified in a systematic review that sought to estimate the health economic cost of T2DM treatment estimates[39]. The cost of liver transaminitis and rhabdomyolysis were drawn accordingly from NHS reference costs 2014/15[34]. The cost of rhabdomyolysis was calculated as a weighted average cost of resource use related to the severity of a rhabdomyolysis event (life threatening, hospitalisation, death or disability) and the percentage of patients experiencing each during a rhabdomyolysis event.

## 2.4. Utilities

Utility estimates for the model health states and adverse events were identified where possible, from a literature search of systematic reviews, relating to the patient event. Utility estimates assessed from the European Quality of Life-5 Dimension-3 Level (EQ-5D-3L) questionnaire, derived from UK time trade-off values, was preferred.

The baseline utility estimate for patients in the disease-free survival state was based upon baseline EQ-5D-EL data of 41 patients undergoing esophagostomy or total gastrectomy, entering a RCT feasibility study. Mean utility was estimated using UK time trade-off values, and was assumed from the study in the model as 0.80[40]. The utility of EAC recurrence was estimated by Boer et al.[41], using standard gamble techniques, from a cohort of 50 patients, interviewed, following esophagetomy for EAC with an average age of 63 years.

Estimates of the utility of abnormal liver function tests were calculated by Donnan et al.[42] from a cohort of 99 UK patients, answering the EQ-5D-3L questionnaire. The utility of type 2 diabetes mellitus (T2DM) was identified from a systematic review conducted reporting T2DM utilities for economic models[43]. The measure of utility from the systematic review were estimates obtained from the United Kingdom Diabetes Study (UKPDS) to measure the utilities of type 2 diabetic patients[44]. As no utility estimate of rhabdomyolysis was found, in line with the assumptions drawn by Mitchell et al.[45], it was assumed the utility value would be comparable to severe myopathy[46]. The disutility was assumed from Mitchell et al.[45] and is presented in table 2, along with a summary of all utilities included in the model.

## 2.5. Analyses performed

The cost-effectiveness result was calculated in terms of expected costs and QALYs. If there was a dominant alternative associated with lower costs and equivalent or better QALY outcomes, this alternative would be highlighted, and no incremental cost-effectiveness ratio (ICER) would be presented. Only if one alternative was associated with better QALY outcomes and increased costs, the expected cost per QALY gained was calculated. i.e. the ICER.

Uncertainty was incorporated into the model through one-way sensitivity analysis, on the cost of statins, follow-up, EAC recurrence and on the expected DFS rate, with incremental cost and QALYs only being measured. An alternative scenario analysis on the risk, cost and utility of rhabdomyolysis was estimated, as well as a scenario allowing for 25% non-adherence. Probabilistic sensitivity analysis (PSA) was performed by replacing base-case estimates for key parameters with probability distributions and sampling values from these distributions over 5000 iterations. The PSA was conducted with a normal distribution around the hazard ratio of statin

therapy. Beta distributions were assumed around the probabilities of an adverse event occurring, and the associated utility values. A gamma distribution with a shape parameter of 1 was conducted on the costs associated with statin treatment and the costs associated with EAC recurrence and death. Uncertainty was reported in terms of 95% confidence intervals around key outcomes and graphically with a cost-effectiveness acceptability curve (CEAC). We also report the probabilities that a statin strategy was dominated (greater costs, worse QALY outcomes), cost-saving (lower costs, equivalent or better QALY outcomes) or cost-effective relative to the NICE £20,000 threshold. Additionally, we report the expected value of perfect information (EVPI) [47]. Finally, we estimate the net budget impact of statins for each 1,000 patients treated.

## 3. RESULTS

### 3.1. Base-Case Results

In the base-case analysis, statins appeared to be the dominant therapy, and therefore a cost-saving treatment of £6,781 (95% CI: £12,471; £1,375) (See Table 3). Including the costs of treatment, statin patients led to greater costs per patient of £487 due to adverse events occurring and follow-up appointments. However, statins led to a decrease of £7,268 in EAC recurrence costs. Lifetime expected QALYs per patient was 4.93 with statins and 3.25 without statins, representing a gain of 1.68 (95% CI: 0.12; 4.41) QALYs per patient prescribed statins. The budget impact analysis suggested net savings of £6.40 million (95% CI: £12.47m; - £1.38m) for each 1,000 EAC patients receiving statin therapy. With respect to recurrences and adverse events, statins were associated with a decrease of 269 EAC recurrences and 20 additional cases of transaminitis, 34 cases of diabetes mellitus per 1,000

patients and 0.43 cases of rhabdomyolysis, including 0.04 deaths, per 10,000

patients. The expected value of perfect information was estimated as £3.07 per

patient.

### 3.2.    Sensitivity Analysis

Consistent with the base-case results, the probabilistic sensitivity analysis suggested

a 98.94% probability that statins were cost-effective relative to a £20,000 per QALY

gained threshold, a 98.86% probability of being cost-saving, and only a 0.36%

probability that the statin alternative was dominated (more costly and less effective).

These probabilistic results are illustrated in the scatter plot in Figure 3.

One-way sensitivity analysis showed that substituting the highest cost statin was still

associated with cost savings and QALY gains with statins (-£4,545; 1.68 QALYs),

and threshold analysis showed that a statin strategy would meet a £20,000 per

QALY gained threshold at an annual statin cost of up to £6,406 (£534 per month) or

a hazard ratio as high as 0.99.  Decreasing the modelled expected disease-free

survival curve of the benefit of statins (Fig.2), by 50%, from 34% to 17%, improved

cost savings and QALY gains (-£8,659; 2.18 QALYs) whilst increasing it by 50%,

from 34% to 51%, reduced savings and QALY gains (-£2,151; 0.35 QALYs) but

statins remained a dominant strategy under both scenarios. Where the cost of

palliative care was halved, the cost saving result also decreased (-£3,651; 1.68).

Finally, a scenario analysis of doubling the cost of follow-up and halving the cost of

EAC recurrence showed statins remained cost saving and led to QALY gains (-

£6,136; 1.68). An alternative scenario analyses of doubling the incidence, mortality

and the cost of rhabdomyolysis and halved its utility did not change the dominance of

statins (-£6,778; 1.68 QALYs). Allowing for non-adherence by assuming 25% of

patients did not take the drugs they received did not change the overall results. The results from the one-way sensitivity analyses are presented in Table 4.

## 4. DISCUSSION

Following esophagectomy and current peri-operative treatment modalities, there are no trial data to support longer-term adjuvant therapies to reduce the risk of recurrence and improve the prognosis in patients with EAC. Based on the recent pharmacoepidemiological data demonstrating large reductions in esophageal cancer-specific and all-cause mortality with statin use post-diagnosis of EAC[14], we modelled the cost-effectiveness of statin therapy alongside standard treatment in preventing recurrence and/or death. The results suggest that statin use in patients' following resection of EAC improve outcomes and if proven to be effective in a future trial, represents very favourable value for money. Indeed, the model suggests that statin therapy could save the NHS £6,781 per patient, or £6.40 million for every 1,000 patients with EAC. Whilst monetary cost savings to the NHS have clearly been highlighted, the reduction in the number of EAC recurrences could have further implications on resource use and capacity within secondary care. Increases in productivity through a reduction in chemotherapy and radiotherapy treatments are potential resource impacts that providers within the NHS could consider.

We performed a number of validation checks consistent with the Assessment of the Validation Status of Health Economic (AdViSHE) decision models checklist[48]. The face validity of the conceptual model and input data were confirmed by experienced gastroenterologists. Extreme values were tested against expected outcomes and check sums were used to trace the initial cohort through the model logic. The model structure was validated against a similar model of statins in the chemoprevention in

Barrett's Esophagus [49]. Finally, the face validity of the final estimates, including costs and survival, were assessed by clinical experts.

To our knowledge, this is the only study presenting the results of the cost-effectiveness of statins alongside standard treatment following esophagectomy with curative intent for EAC. Given the 98.86% probability of the cost-saving result and 98.94% probability of statins being cost-effective in probabilistic sensitivity analysis, assuming causality, we believe the results we present are robust. This is supported by the sensitivity analyses that consistently showed that statins represented strong value for money across a range of assumptions and parameter values. In absence of definitive evidence around the cost of follow-up and cost of recurrence, even when both were adjusted to double the parameter values, statins continued to remain cost-saving. Additionally, the sensitivity analyses conducted also suggests that statins leads to gains in QALYs.

There are a number of limitations in the analysis. Firstly, we are aware the model did not include the related CVD benefits due to statin exposure. As statins reduce mortality, the health care related costs accrued due to additional life years, should be modelled. Arguably, other conditions associated with advanced age, such as dementia and hip fracture are leading causes of mortality, and may account for possible future medical costs, that should also be modelled. As the aim of the cost-effectiveness is to inform the efficacy of statin therapy in patients with EAC, and to limit the scope to the condition of interest, we simplified the model to exclude the related CVD benefits.

A second limitation is the assumption of the primary measure of benefit being informed from epidemiological population-data[14]. While the roles of reverse

causation bias and unmeasured confounding cannot be excluded, such observational research is the highest level of available evidence (there are no current trial data) on which to base this economic analysis. Even if the assumed effect size of statin therapy (HR=0.63) is an overestimate, adjuvant statin therapy remains cost-effective assuming much lower estimates of effect size with statin treatment (i.e. HR = 0.99). In modelling the EAC-mortality and all-cause mortality rates from observational data, we assumed the effect size of statins was applicable to patients following surgery for EAC and reflects the effect of statins on disease free survival. While the low EVPI of £3.07 suggests that there would be little value in refining the estimates of effect size from observational data alone; to change clinical practice and include the adjuvant treatment of EAC as a new licenced indication for statins would require a phase III RCT, hence superseding the value of EVPI alone. The safety profile of statins is well described and favourable. However, factors other than EVPI, such as the clinical evidence of the disease area are reported to have potential weight on recommendations for further research, and should be carefully considered[50].

## 5.  CONCLUSIONS
Statin therapy for patients following potentially curative resection of EAC appears to reduce NHS cost, assuming there is a casual reduction in the risk of cancer recurrence and of death.

**Data Availability Statement:** The data and model are available on request from the corresponding author.

# REFERENCES

[1.    Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, and Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012. Int J Cancer. 2015 Mar 1;136(5):E359–86.

[2]    Cancer Research UK, 'Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK'. 2013.

[3]    C. Lepage, B. Rachet, V. Jooste, J. Faivre, and M. P. Coleman, 'Continuing Rapid Increase in Esophageal Adenocarcinoma in England and Wales', *Am. J. Gastroenterol.*, vol. 103, no. 11, pp. 2694–2699, Nov. 2008.

[4]    M. Arnold, I. Soerjomataram, J. Ferlay, and D. Forman, 'Global incidence of oesophageal cancer by histological subtype in 2012', *Gut*, vol. 64, no. 3, pp. 381–387, Mar. 2015.

[5]    G. Edgren, H.-O. Adami, E. Weiderpass Vainio, and O. Nyren, 'A global assessment of the oesophageal adenocarcinoma epidemic', *Gut*, vol. 62, no. 10, pp. 1406–1414, Oct. 2013.

[6]    National Audit Office, 'Progress in improving stroke care: Report on the findings from our modelling of stroke care provision.'

[7]    van Hagen P, Hulshof MCCM, van Lanschot JJB, Steyerberg EW, Henegouwen MI van B, Wijnhoven BPL, Richel DJ, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta, MA, Blaisse RJB, Busch ORC, ten Kate FJW, Creemers G-J, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. N Engl J Med. 2012 May 31;366(22):2074–84.

[8]    NICE guidelines CG181, 'Cardiovascular disease: risk assessment and reduction, including lipid modification'. Jul-2014.

[9]    O. O. Ogunwobi and I. L. P. Beales, 'Statins Inhibit Proliferation and Induce Apoptosis in Barrett's Esophageal Adenocarcinoma Cells', *Am. J. Gastroenterol.*, vol. 103, no. 4, pp. 825–837, Apr. 2008.

[10] M. R. Sadaria *et al.*, 'Statin therapy attenuates growth and malignant potential of human esophageal adenocarcinoma cells', *J. Thorac. Cardiovasc. Surg.*, vol. 142, no. 5, pp. 1152–1160, Nov. 2011.

[11] F. Ye, 'Suppression of esophageal cancer cell growth using curcumin, (-)-epigallocatechin-3-gallate and lovastatin', *World J. Gastroenterol.*, vol. 18, no. 2, p. 126, 2012.

[12] P. C. Konturek, G. Burnat, E. G. Hahn, and others, 'Inhibition of Barrett's adenocarcinoma cell growth by simvastatin: involvement of COX-2 and apoptosis-related proteins', *J. Physiol. Pharmacol.*, vol. 58, p. 141, 2007.

[13] Z. Mei, M. Liang, L. Li, Y. Zhang, Q. Wang, and W. Yang, 'Effects of statins on cancer mortality and progression: A systematic review and meta-analysis of 95 cohorts including 1,111,407 individuals: Statins on cancer mortality and progression', *Int. J. Cancer*, vol. 140, no. 5, pp. 1068–1081, Mar. 2017.

[14] L. Alexandre, A. B. Clark, H. Y. Bhutta, S. S. M. Chan, M. P. N. Lewis, and A. R. Hart, 'Association Between Statin Use After Diagnosis of Esophageal Cancer and Survival: a Population-based Cohort Study', *Gastroenterology*, Jan. 2016.

[15] L. Alexandre *et al.*, *PWE-109 A Feasibility study of adjuvant statin therapy in the prevention of post-operative recurrence of oesophageal adenocarcinoma (The STAT-ROC Feasibility Study)*. BMJ Publishing Group, 2017.

[16] G. Chadwick *et al.*, 'National Oesophago-Gastric Cancer Audit. 2016', 2016.

[17] NICE guidelines. Guide to the methods of technology appraisal 2013: Process and methods guides. (NICE article [PMG9]).

[18] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. N Engl J Med. 2006 Jul 6;355(1):11–20.

[19] W. Weibull, 'A Statistical Distribution Function of Wide Applicability', *ASME J. Appl. Mech.*, vol. 18, pp. 293–297, Sep. 1951.

[20] H. Akaike, 'A new look at the statistical model identification', *IEEE Trans. Autom. Control*, vol. 19, no. 6, pp. 716–723, Dec. 1974.

[21] A. Komogorov, 'Sulla determinazione empirica di una legge di distribuzione.', *G Ist Ital Attuari*, vol. 4, pp. 83 – 91, 1933.

[22] J. Armitage, 'The safety of statins in clinical practice', *The Lancet*, vol. 370, no. 9601, pp. 1781–1790, Nov. 2007.

[23] J. A. Finegold, C. H. Manisty, B. Goldacre, A. J. Barron, and D. P. Francis, 'What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice', *Eur. J. Prev. Cardiol.*, vol. 21, no. 4, pp. 464–474, Apr. 2014.

[24] Cholesterol Treatment Trialists' (CTT) Collaboration, 'Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials', *The Lancet*, vol. 376, no. 9753, pp. 1670–1681, Nov. 2010.

[25] A. Tiwari, V. Bansal, A. Chugh, and K. Mookhtiar, 'Statins and myotoxicity: a therapeutic limitation', *Expert Opin. Drug Saf.*, vol. 5, no. 5, pp. 651–666, Sep. 2006.

[26] P. D. Thompson, 'Statin-Associated Myopathy', *JAMA*, vol. 289, no. 13, p. 1681, Apr. 2003.

[27] P. D. Thompson, G. Panza, A. Zaleski, and B. Taylor, 'Statin-Associated Side Effects', *J. Am. Coll. Cardiol.*, vol. 67, no. 20, pp. 2395–2410, May 2016.

[28] P. Clarke, A. Gray, R. Legood, A. Briggs, and R. Holman, 'The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65).', *Diabet. Med. 206*, p. :pp. 442–450, 2003.

[29] World Health Organization, '2008-2013 Action Plan for the Global Strategy for the Prevention and Control of noncommunicable Diseases.', 2008.

[30] Office for National Statistics, 'National Life Tables, Great Britain, Based on data for the years 2011-2013', Sep. 2014.

[31] N. F. Saba and B. F. El-Rayes, Eds., *Esophageal Cancer*. Cham: Springer International Publishing, 2015.

[32] L. CURTIS, *UNIT COSTS OF HEALTH AND SOCIAL CARE.* S.l.: UNIVERSITY OF KENT, 2016.

[33] Joint Formulary Committee, 'British National Formulary (online) London: BMJ Group and Pharmaceutical Press'. 2016.

[34] 'NHS Reference Costs, 2014/15'. .

[35] The National Institute for Health and Care Excellence., 'Capecitabine for the treatment of advanced gastric cancer. Technology appraisal guidance [TA191].' 28-Jul-2010.

[36] The Royal College of Surgeons of England, 'National Oesophago-Gastric Cancer Audit, 2013'. 2013.

[37] K. Thomas, H. Corner, and M. Stobbart-Rowlands, 'National primary care audit in end of life care and ACP and recommendations for improvement', *BMJ Support. Palliat. Care*, vol. 2, no. 2, pp. 192.3–192, Jun. 2012.

[38] N. Hex, C. Bartlett, D. Wright, M. Taylor, and D. Varley, 'Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs: Estimating current and future costs of Type 1 and Type 2 diabetes in the UK', *Diabet. Med.*, vol. 29, no. 7, pp. 855–862, Jul. 2012.

[39] Liebl, K. Khunti, D. Orozco-Beltran, and J.-F. Yale, 'Health Economic Evaluation of Type 2 Diabetes Mellitus: A Clinical Practice Focused Review', *Clin. Med. Insights Endocrinol. Diabetes*, p. 13, Mar. 2015.

[40] D. J. Bowrey *et al.*, 'A randomised controlled trial of six weeks of home enteral nutrition versus standard care after oesophagectomy or total gastrectomy for cancer: report on a pilot and feasibility study', *Trials*, vol. 16, no. 1, Dec. 2015.

[41] A. G. E. M. de Boer *et al.*, 'Transhiatal vs extended transthoracic resection in oesophageal carcinoma: patients' utilities and treatment preferences', *Br. J. Cancer*, vol. 86, no. 6, pp. 851–857, Mar. 2002.

[42] P. Donnan *et al.*, 'Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE)', *Health Technol. Assess.*, vol. 13, no. 25, Apr. 2009.

[43] A. Beaudet, J. Clegg, P.-O. Thuresson, A. Lloyd, and P. McEwan, 'Review of Utility Values for Economic Modeling in Type 2 Diabetes', *Value Health*, vol. 17, no. 4, pp. 462–470, Jun. 2014.

[44] P. Clarke, A. Gray, and R. Holman, 'Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62)', *Med. Decis. Making*, vol. 22, no. 4, pp. 340–9, Aug. 2002.

[45] D. Mitchell, J. Guertin, A. Iliza, and J. LeLorier, 'Economic Evaluation Of A Pharmacogenomic Test For Statin-Induced Myopathy In Cardiovascular High-Risk Patients Initiating A Statin', *Value Health*, vol. 18, no. 7, p. A396, Nov. 2015.

[46] C. A. Hutchison, K. Patel, and T. Whitehouse, 'Early survival and duration of hospital admission in rhabdomyolysis: ICNARC Case Mix Programme Database', *Crit. Care*, vol. 15, no. 6, p. 452, 2011.

[47] A. H. Briggs, K. Claxton, and M. J. Sculpher, *Decision modelling for health economic evaluation*. Oxford: Oxford University Press, 2006.

[48] P. Vemer, I. Corro Ramos, G. A. K. van Voorn, M. J. Al, and T. L. Feenstra, 'AdViSHE: A Validation-Assessment Tool of Health-Economic Models for Decision Makers and Model Users', *PharmacoEconomics*, vol. 34, no. 4, pp. 349–361, Apr. 2016.

[49] S. E. Choi, K. E. Perzan, A. C. Tramontano, C. Y. Kong, and C. Hur, 'Statins and Aspirin for Chemoprevention in Barrett's Esophagus: Results of a Cost-Effectiveness Analysis', *Cancer Prev. Res. (Phila. Pa.)*, vol. 7, no. 3, pp. 341–350, Mar. 2014.

[50] J. Thorn, J. Coast, and L. Andronis, 'Interpretation of the Expected Value of Perfect Information and Research Recommendations: A Systematic Review and Empirical Investigation', *Med. Decis. Making*, vol. 36, no. 3, pp. 285–295, Apr. 2016.

[51] M. Law and A. R. Rudnicka, 'Statin Safety: A Systematic Review', *Am. J. Cardiol.*, vol. 97, no. 8, pp. S52–S60, Apr. 2006.

# TABLES

Table 1: Key-input parameter estimates.

| Input Parameters | Rate* (SD) | Active statin** (SD) | PSA Distribution | Rate source |
|---|---|---|---|---|
| *Mortality* | | | | |
| Baseline EAC mortality | 42.20% | | | Alexandre et al, 2016; T3[14] |
| HR(EAC mortality)\|statin | 0.61 | | Normal (95%CI: 0.38 – 0.96) | Alexandre et al, 2016; T3[14] |
| Baseline all-cause mortality | 66.50% | | | Alexandre et al, 2016; T3[14] |
| HR(all-cause mortality)\|statin | 0.63 | | Normal (95%CI: 0.43 – 0.92) | Alexandre et al, 2016; T3[14] |
| | | | | |
| ***Adverse events*** | | | **(α,β)** | |
| | | | | |
| Liver tranasminases >3ULN | 0.3757% | 0.4945% | Beta, (7.191,594.809) | Finegold, 2014; T2[23] |
| Diabetes mellitus | 0.6892% | 0.8609% | Beta, (13.142,588.858) | Finegold, 2014; T2[23] |
| Rhabdomyolysis | 0.0000% | 0.0054% | Beta, (0.0787,601.921) | Law, 2006; T3[51] |

EAC = Esophageal adenocarcinoma; HR = Hazard Ratio; ULN = Upper limit normal

(Liver transaminases occurs when the transaminases alanine transaminase (ALT) is

greater than 3 times the ULN; T2 = Table 2 (Data drawn from table 2 in the source

article); T3 = Table 3 (Data drawn from table 3 in the source article).

*The Rate describes the baseline risk parameters of patients inputted into the model,

without statin therapy.

**The Active Statin describes the risk parameters of patients inputted into the model,

reflecting stating therapy.

Table 2: Unit costs, utilities and sources.

| Unit costs and utilities | Annual Cost (£) | PSA distribution (k, θ) | Source |
|---|---|---|---|
| *Costs* | | | |
| Statins | £34.15 | Gamma, (34.15,1) | BNF 2015[33] |
| Follow-up, years 1-2 | £334.00 | Gamma, (334.00,1) | NHS Reference Costs 2014/15 (HRG:WF01A)[34] |
| Follow-up, years 3-5 | £167.00 | Gamma, (167.00,1) | NHS Reference Costs 2014/15 (HRG:WF01A)[34] |
| EAC recurrence | £3,685.62 | Gamma, (3,685.62,1) | NHS Reference Costs 2014/15, TA191[34], [35] |
| Palliative Care | £24,181.00 | Gamma, (24,181.00,1) | |
| Liver Transaminases >3ULN | £1,686.00 | Gamma, (1,686.00,1) | NHS Reference Costs, 2014/15 (HRG:GC17K)[34] |
| Diabetes Mellitus | £513.54 | Gamma, (513.54,1) | Hex et al, 2012[38] |
| Rhabdomyolysis | £5,300.62 | Gamma, (5,300.62,1) | NHS Reference Costs, 2014/15 (HRG:AA35F)[34] |

| | Utility | PSA distribution (α,β) | Source |
|---|---|---|---|
| *Utilities* | | | |
| Disease-free following EAC | 0.80 | Beta, (554.99,47.02) | Bowrey et al, 2015[40] |
| Esophageal cancer recurrence | 0.41 | Beta, (246.82, 355.18) | Boer et al, 2002[41] |
| Liver transaminases >3ULN | 0.79 | Beta, (475.58, 126.42) | Donnan et al, 2009[42] |
| Diabetes mellitus | 0.79 | Beta, (472.57, 129.43) | Clarke et al, 2002[44] |
| Rhabdomyolysis | 0.14 | Beta, (84.28, 517.72) | Mitchell et al, 2015[45] |

EAC = Esophageal adenocarcinoma; HR = Hazard ratio; ULN = Upper limit normal
(Liver transaminases occurs when the transaminases alanine transaminase (ALT) is
greater than 3 times the ULN.

Table 3: Base case results: expected cost and QALYs per patient

|  | Statin Therapy | No Statin Therapy | Difference |
|---|---|---|---|
| Total Costs (per patient) | £12,265 | £19,046 | -£6,781 (95% CI: £12,471; £1,375) |
| Follow-Up costs | £814 | £674 | £140 |
| Statin-drug costs | £216 | - | £216 |
| Statin-related AE costs | £258 | £127 | £131 |
| EAC recurrence costs | £10,977 | £18,245 | -£7,268 |
| QALYs | 4.93 | 3.25 | 1.68 (95% CI: 0.12; 4.41) |
| ICER (£/QALY) | Cost Saving | Dominated | |

AE = Adverse events; EAC = Esophageal adenocarcinoma; QALYs = Quality
adjusted life years; ICER = Incremental cost effectiveness ratio.

Table 4: Deterministic Sensitivity Analyses results

|  | Cost | QALY |
|---|---|---|
| Highest Price of Statins = £387 | -£4,545 | 1.68 |
| Cost of follow up increases by 50% and EAC recurrence reduced by 50% | -£6,136 | 1.68 |
| HR\|(EAC mortality) Statins = 0.99 | -£32 | 0.04 |
| Cost of palliative care reduced by 50% | -£3,651 | 1.68 |
| Double the cost of rhabdomyolysis, the baseline risk and disutility | -£6,778 | 0.84 |
| DFS rate decreases by 50% (34% to 17%) | -£8,659 | 2.18 |
| DFS rate increases by 50% (34% to 68%) | -£2,151 | 0.35 |

**FIGURES**

**Fig.1**

Figure 1 presents the probabilistic state-transition model as a schematic of the possible health states patients' progress through within each one-year cycle over a lifetime horizon. All patients begin in the disease-free survival health state, and can either remain in that state, have an EAC recurrence, or death due to background mortality or due to EAC. Once a patient progress' to EAC recurrence, the patient will continue to remain in that state or die due to EAC or due to other mortalities.
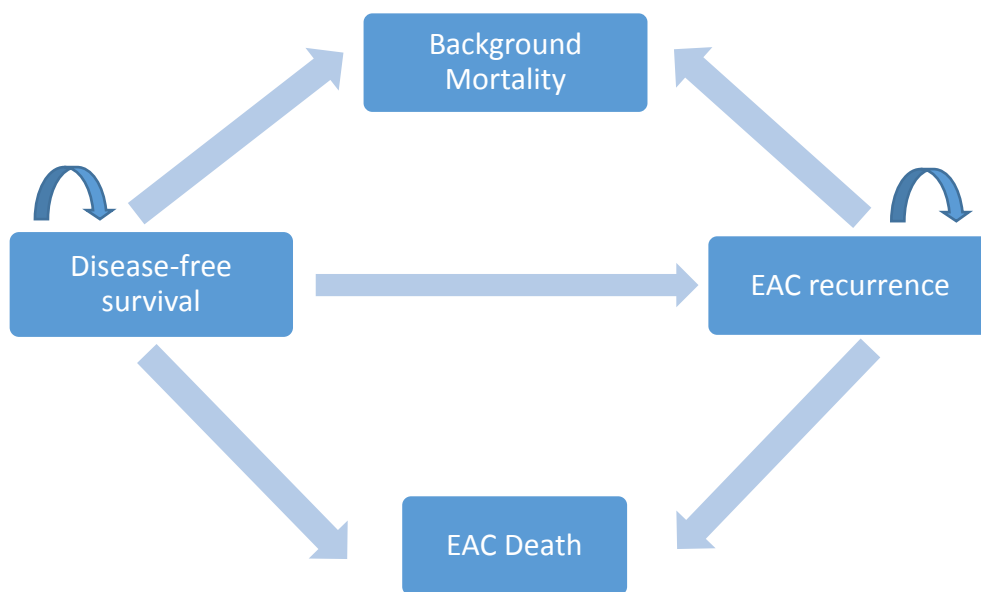
**Fig.2**

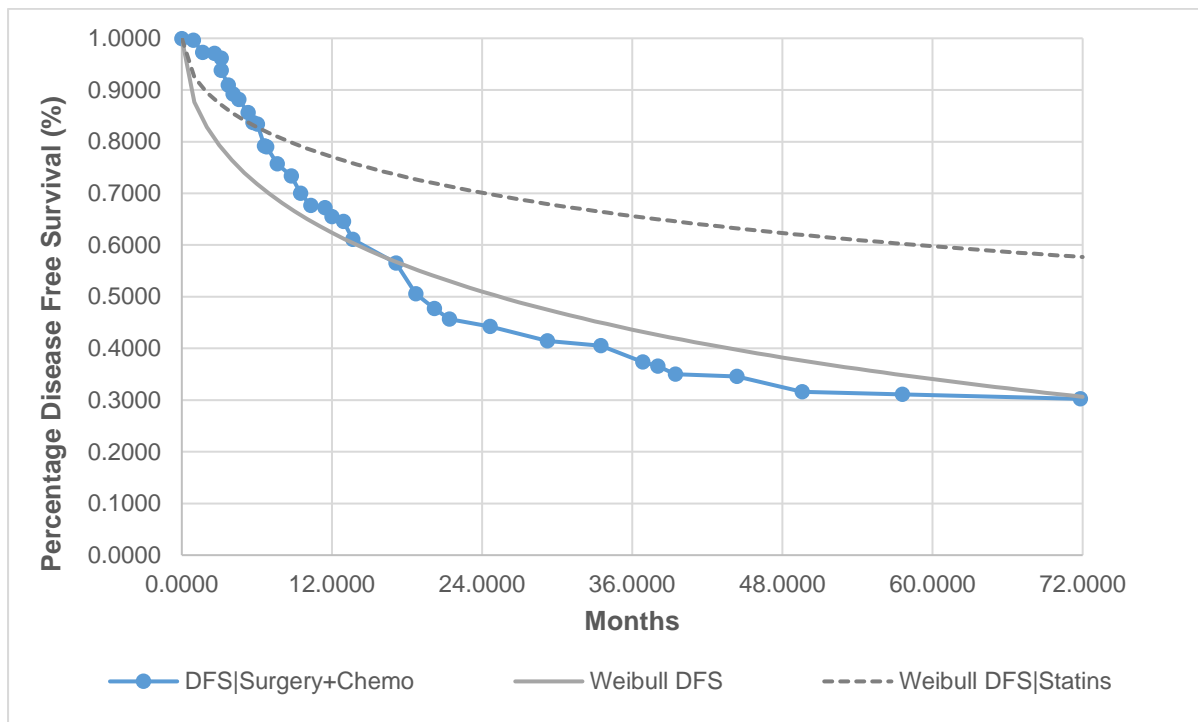Modelled Kaplan-Meier Estimates of Disease-free Survival and fitted curves.

**Fig.3.**

Incremental cost-effectiveness plane of Statin use versus no statin use. Each point represents the incremental cost-effectiveness ratio (ICER), drawn from each of the 5000 iterations in probabilistic sensitivity analysis.