TECHNICAL APPENDIX 1: ECONOMIC MODEL VARIABLES

1 RESOURCE UTILISATION AND COST VARIABLES

The methods associated with the estimation of resource utilisation and treatment costs are presented by category.

1.1 RADIOTHERAPY TREATMENT

In order to calculate the total cost of radiotherapy treatment, both the type of radiotherapy regimen received (once daily, twice daily or concomitant boost) and the actual number of fractions received by each patient are required. The valuation of the radiotherapy regimens is dictated by the way radiotherapy unit costs are currently reported. The NHS Reference Costs (Department of Health, 2005) present radiotherapy unit costs that are grouped by complexity level and number of fractions. Due to the groupings it is not possible to calculate the cost on a strictly per fraction basis. **Table 1** presents the available radiotherapy unit costs by health related group (HRG).

Table 1 Radiotherapy unit costs

HRG Code	HRG Label	No. of Courses of Treatment	National Average Unit Cost (£)	Interquartile Range of Unit Costs (£)	
				Lower Quartile	Upper Quartile
w01	Superficial Teletherapy, <4 Fractions	5,021	193.22	147.00	321.16
w02	Superficial Teletherapy, >3 Fractions	3,438	530.73	355.69	700.50
w03	Simple Teletherapy, <4 Fractions	5,146	279.87	189.28	378.26
w04	Simple Teletherapy, >3 <13 Fractions	5,268	538.77	418.92	791.76
w05	Simple Teletherapy, >12 Fractions	1,136	909.06	744.00	1,299.00
w06	Simple Teletherapy with Simulator, <4 Fractions	19,577	380.21	274.68	528.08
w07	Simple Teletherapy with Simulator, >3 <13 Fractions	18,159	705.41	533.43	939.06
w08	Simple Teletherapy with Simulator, >12 Fractions	5,389	1,219.64	922.45	1,649.70
w09	Complex Teletherapy, <4 Fractions	404	1,037.58	412.70	1,011.12
w10	Complex Teletherapy, >3 <13 Fractions	1,288	829.59	680.24	1,132.86
w11	Complex Teletherapy, >12 <24 Fractions	4,343	1,358.45	1,123.53	2,032.00
w12	Complex Teletherapy, >23 Fractions	2,243	1,619.78	1,429.80	2,708.07
w13	Complex Teletherapy with Imaging, <4 Fractions	632	575.63	490.75	1,044.44
w14	Complex Teletherapy with Imaging, >3 <13 Fractions	2,700	1,118.96	903.35	1,449.00
w15	Complex Teletherapy with Imaging, >12 <24 Fractions	16,888	1,857.71	1,374.61	2,012.25
w16	Complex Teletherapy with Imaging, >23 Fractions	9,666	2,245.50	1,735.92	2,668.91
w17	Complex Teletherapy with Imaging and Multiple Planning, >23 Fractions	2,291	2,635.40	2,103.72	3,293.59
w18	Complex Teletherapy with Imaging, Hyperfraction	109	2,679.24	2,204.17	3,147.87
w19	Complex Teletherapy with Imaging and Multiple Planning,	52	4,078.57	2,397.45	4,636.44

	Hyperfraction				
w20	Teletherapy with Technical Support, <4 Fractions	1,628	919.16	648.86	1,346.59
w21	Teletherapy with Technical Support, >3 <13 Fractions	5,297	1,135.93	851.61	1,554.91
w22	Teletherapy with Technical Support, >12 <24 Fractions	6,010	1,879.77	1,457.54	2,388.88
w23	Teletherapy with Technical Support, >23 Fractions	4,879	2,253.54	1,756.49	3,025.33
w24	Teletherapy with Technical Support and Multiple Planning, >23 Fractions	3,498	3,243.66	2,605.87	3,748.17
w25	Teletherapy with Technical Support, Hyperfractionation	499	2,403.76	1,862.00	3,505.00
w26	Teletherapy with Technical Support and Multiple Planning, Hyperfractionation	363	3,049.22	1,796.17	4,882.06

Source: Reference Costs 2004.

Given the multitude of radiotherapy HRGs, it was important to establish which are appropriate for this patient population. Expert advice was sought from a clinical oncologist (personal communication, Dr Tova Prior, University College Hospital London), who indicated that patients in this population will be immobilised in a shell, meaning that technical support definitely applies as defined by the NHS Reference Costs:

Technical Support; Any treatment irrespective of complexity or beam energy which requires individually crafted items for specific patients such as casts, shells or other individually produced positioning devices or individually crafted beam shapers or modifiers. Includes techniques such as whole or hemibody irradiation that produce major disruption to routine practice with special positioning or dose measuring problems. Also includes teletherapy treatments which require anaesthetic and conformal radiotherapy using cast shells and stereotactic radiotherapy. Excludes use of thermoplastic materials. (NHS Data Dictionary & Manual)

Therefore the HRG costs listed in **Table 1** that apply to technical support were carried forward to the analysis. These unit costs were applied according to the radiotherapy regimen and/or number of fractions received by each patient as applicable. Where more than one HRG is available, a weighted average is applied. **Table 2** presents the unit costs of radiotherapy treatment applied in each case.

Table 2 Radiotherapy costs applied to economic model

Once daily radiotherapy, less than 4 fractions received			
Applicable HRGs (<4 fractions)	*Unit cost*	*# of courses*	***(Weighted) mean cost*** **£919.16**
HRG w20 Teletherapy with Technical Support, <4 Fractions	£919.16	1,628	
Once daily radiotherapy, between 4 and 12 fractions received			
Applicable HRGs (>3, <13 fractions)	*Unit cost*	*# of courses*	***(Weighted) mean cost*** **£1,135.93**
HRG w21 Teletherapy with Technical Support, >3 <13 Fractions	£1,135.93	5,297	
Once daily radiotherapy, between 13 and 23 fractions received			
Applicable HRGs (>12, <24 fractions)	*Unit cost*	*# of courses*	***(Weighted) mean cost*** **£1,879.77**
HRG w22 Teletherapy with Technical Support, >12 <24 Fractions	£1,879.77	6,010	

Once daily radiotherapy, greater than 23 fractions received			
Applicable HRGs (>23 fractions)	*Unit cost*	*# of courses*	
HRG w23 Teletherapy with Technical Support, >23 Fractions	£2,253.54	4,879	***Weighted mean cost*** **£2,666.99**
HRG w24 Teletherapy with Technical Support and Multiple Planning, >23 Fractions	£3,243.66	3,498	
Twice daily or concomitant boost radiotherapy			
Applicable HRGs (hyperfractionation)	*Unit cost*	*# of courses*	
HRG w25 Teletherapy with Technical Support, Hyperfractionation	£2,403.76	499	***Weighted mean cost*** **£2,675.57**
HRG w26 Teletherapy with Technical Support and Multiple Planning, Hyperfractionation	£3,049.22	363	

The pattern of use reported for the above HRGs corresponds to the pattern of use reported by the UK Expert Panel, with hyperfractionation making up a small percentage of the total number of courses. The weighted average of the hyperfractionation HRGs was applied in the model to those patients who received either twice daily or concomitant boost radiotherapy in the clinical trial. The cost applied to those patients who received once daily radiotherapy depended on the actual number of fractions received in the trial. In the vast majority of cases, patients received more than 23 fractions and therefore were assigned the cost of approximately £2,700, however, there were a few cases who received less. The method for applying costs of radiotherapy is the same for patients in both treatment groups

1.2 CETUXIMAB ACQUISITION

The trial dataset recorded the exact dose of cetuximab administered to each patient in the ERT group during the acute treatment phase. In England and Wales, cetuximab is available in a single size vial (100 mg) priced at £136.50 (British National Formulary (BNF) 50). The dosage schedule is as follows:

- 400 mg/m^2 loading dose in week 1, followed by 250 mg/m^2 for the next 6-7 weeks

The dose depends on the body surface area of each individual patient. For each administration, wastage is included in the model calculation as the dose is rounded up to the nearest hundred mg and divided by 100 to arrive at the required number of vials. This process is repeated for each administration and the total cost aggregated for each patient.

1.3 THERAPY ADMINISTRATION FOR RT PATIENTS

An estimation of the type and cost of radiotherapy administration was estimated based on clinical expert advice (UK Expert Panel). It was indicated that radiotherapy is always administered on an outpatient basis, with individual administrations consisting only of the small amount of time required for the technical delivery of treatment. Contact time with the specialist was estimated to be approximately 1 session per week of approximately 15 minutes each, which did not vary by regimen.

The three regimens used in the study are as follows:

- **Once daily**: 35 fractions, 5 fractions/per week for 7 weeks
- **Twice-daily**: 60-64 fractions, 10 fractions per week for 6-6.5 weeks
- **Concomitant boost**: 42 fractions, 5 fractions per week for 3.5 weeks then 10 fractions per week for 2.5 weeks

A conservative estimate of 1 outpatient visit per week during treatment is applied to the economic model for all RT patients. **Table 3** presents all the administration unit cost values applied to the economic model.

Table 3 Treatment administration unit costs

Setting		**Cost**	**Reference**
Radiotherapy administration	Initial outpatient visit	£141.61	Outpatient specialty code RADY (No treatment) - Initial visit
	Subsequent outpatient visit	£88.31	Outpatient specialty code RADY (No treatment) - Subsequent visit
Cetuximab administration	Initial outpatient visit	£178.66	Outpatient specialty code 370 (Medical Oncology) - Initial visit
	Subsequent outpatient visit	£124.66	Outpatient specialty code 370 (Medical Oncology) - Subsequent visit

Source: Reference Costs 2004.

1.4 THERAPY ADMINISTRATION FOR ERT PATIENTS

The cost of administration for patients in the ERT group is estimated in a similar manner to that in the RT group, with two notable exceptions. Firstly, the administration schedule for cetuximab - as noted in the summary product characteristics - is once per week intravenously over a period of approximately one hour. Therefore it is assumed that cetuximab can be administered within an outpatient setting. Patients are assigned the full cost of a medical oncology outpatient visit for cetuximab administration (**Table 3**) in addition to the cost of the radiotherapy administration.

Secondly, the acute treatment phase of the pivotal trial was 1-2 weeks longer in duration for ERT patients than for RT patients depending on their radiotherapy regimen. Extra outpatient administration visit costs were included for ERT patients for administrations received following the end of radiotherapy treatment.

1.5 TREATMENT-EMERGENT ADVERSE EVENTS

Grade 3 or 4 AEs were reported in 179 (84.4%) patients in the RT alone group and in 188 (90.4%) patients in the ERT group. Frequencies were comparable between the 2 treatment groups, apart from acne, which is a known side effect of cetuximab. Thus, concomitant cetuximab does not seem to aggravate the toxicity of RT. Nonetheless, a detailed cost analysis of the reported adverse events in the clinical trial dataset was performed.

Due to the nature of the reporting of adverse effects of treatment in the trial dataset, there were a number of complexities associated with calculating the cost of treatment of the events on a patient level basis. Firstly, the size of this part of the dataset made analysis of each event prohibitive. The dataset reports 8,207 separate patient events across both treatment groups, comprising over 300 types of event by COSTART definition. In order to make the analysis manageable, some assumptions as to the cost importance of adverse events were applied to the dataset. Clinical expert opinion (personal communication, Prof Chris Boshoff, University College Hospital London) was sought to identify those adverse events which were likely to be the most significant cost drivers, with respect to a combination of the frequency of occurrence and the intensity of resources required for treatment. The expert advice indicated that the following adverse events (with severity defined by their associated NCI CTC toxicity grades) were assumed to be of the greatest cost importance:

- Acne or Rash, grade 3 or 4
- Anaemia, grade 3 or 4
- Dehydration, grade 3 or 4
- Dry Mouth, grade 3 or 4
- Febrile Neutropenia, grade 3 or 4
- Fever or Infection, grade 3 or 4
- Leucopenia, grade 3 or 4
- Mucositis, Stomatitis or Dysphagia, grade 2, 3 or 4
- Nausea and Vomiting, grade 2, 3 or 4
- Radiation Dermatitis, grade 3 or 4

- Thrombocytopenia, grade 3 or 4
- Weight loss, grade 3 or 4

Expert advice indicated that, it was possible to group mucositis, stomatitis and dysphagia together for cost purposes and to do similar with acne and rash. Given that the above listed events account for approximately 64% of all patient events recorded in the database, it is assumed that the remaining approximately 280 other types of event are rare and do not occur sufficiently often that their omission would bias the cost analysis.

Secondly, the recording of end dates of each event was often incomplete. Ideally, the analysis would have been able to account for the exact length of each included patient event and calculate the cost accordingly. However the extent of missing end dates was such that this approach was not practical. Instead, events were treated on an average episode basis whereby costs were applied as per what would be expected for each type of event and severity grade. For England and Wales, estimates were drawn from the UK Expert Panel to estimate cost parameters including the likelihood of hospital admission, medication, procedures etc. **Table 4** presents the estimates of the expert panel.

Table 4 Estimates of cost parameters of adverse events

Adverse Event	Toxicity Grade	Likelihood of admission	Medication	Procedures
Mucositis/stomatitis/dysphagia	2	5%	Anti-fungal mouth rinse	None
Mucositis/stomatitis/dysphagia	3	10%	Anti-fungal mouth rinse	None
Mucositis/stomatitis/dysphagia	4	100%	Included within HRG	Included within HRG
Nausea/vomiting	2	10%	Anti-emetics	None
Nausea/vomiting	3	30%	Anti-emetics	None
Nausea/vomiting	4	100%	Included within HRG	Included within HRG
Weight loss	3/4	0%	None	None
Radiation dermatitis	3/4	0%	Topical corticosteroid	None
Dry mouth	3/4	0%	None	None
Fatigue	3/4	0%	None	None
Dehydration	3/4	100%	Included within HRG	Included within HRG
Acne/rash	3/4	0%	Topical and oral anti-bacterial	None
Thrombocytopenia	3/4	0%	None	Platelet transfusion
Febrile neutropenia	3/4	100%	Included within HRG	Included within HRG
Leukopenia	3/4	0%	None	None
Anaemia	3/4	100%	Included within HRG	Included within HRG
Fever/Infection	3/4	50%	Anti-pyretic	None

Source: UK Expert Panel
Key: "Included within HRG", all treatment costs incorporated within HRG admission costs.

The unit costs applicable to the above inputs are presented in **Table 5**.

Table 5 Unit costs of adverse events cost components

Component	Unit cost	Reference & Notes

Hospitalisation		
Anaemia grade 3 or 4	£930.04	NELIP HRG S06 – Red blood cell disorders without complications
Dehydration grade 3 or 4	£1,519.05	NELIP HRG K09 – Disorders of nutrition
Febrile neutropenia grade 3 or 4	£1,337.42	NELIP HRG P23 – Blood cell disorders
Fever/infection grade 3 or 4	£2,206.53	NELIP HRG P05 – Major infections
Mucositis/stomatitis/dysphagia grade 2	£1,818.27	NELIP HRG C37 – Complex major head, neck or ear diagnoses without complications
Mucositis/stomatitis/dysphagia grade 3 or 4	£3,035.70	NELIP HRG C36 – Complex major head, neck or ear diagnoses with complications
Nausea & vomiting grade 2	£702.40	NELIP HRG F47 – General abdominal disorders without complications
Nausea & vomiting grade 3 or 4	£1,099.06	NELIP HRG F46 – General abdominal disorders with complications
Medications		
Anti-fungal mouth rinse	£4.01	BNF 50 - Benzydamine (Difflam) oral rinse, 300 ml
Anti-emetic	£4.86	BNF 50 - Domperidone (generic) 10 mg tabs, pack of 100
Anti-pyretic	£0.21	BNF 50 – Paracetamol (generic) 500 mg tabs, pack of 20
Topical anti-bacterial	£22.24	BNF 50 – Zinc acetate/erythromycin (Zineryt) 90 ml
Oral anti-bacterial	£21.24	BNF 50 Minocycline (Minocin MR) 100 mg tabs, pack of 56
Topical corticosteroid	£6.36	BNF 50 – Betamethasone (Diprosone) 100 mg tube
Procedures		
Platelet transfusion	£84.22	Varney S.J. Guest J.F. The annual cost of blood transfusions in the UK. Transfusion medicine, 2003, 13, 205-218 pp. 207-208

Key: NELIP, non-elective inpatient. HRG, health related group. BNF, British National Formulary.

These values were used to compile expected values for the average episode costs of each adverse event and toxicity grade, which were applied to the analysis (**Table 6**).

Table 6 Average episode costs applied to economic model

Adverse Event	Toxicity Grade	Expected episode cost	How calculated
Mucositis/stomatitis/dysphagia	2	£94.72	HRG C37 multiplied by 5% plus medication[1]
Mucositis/stomatitis/dysphagia	3	£307.18	HRG C36 multiplied by 10% plus medication[2]
Mucositis/stomatitis/dysphagia	4	£3,035.70	HRG C36 multiplied by 100%
Nausea/vomiting	2	£80.68	HRG F47 multiplied by 10% plus medication[3]
Nausea/vomiting	3	£333.29	HRG F46 multiplied by 30% plus medication[4]
Nausea/vomiting	4	£1,099.06	HRG F46 multiplied by 100%
Radiation dermatitis	3/4	£6.36	Cost of tube of betamethasone
Acne/rash	3/4	£43.38	Cost of course of topical and oral anti-bacterials
Dehydration	3/4	£1,519.05	HRG K09 multiplied by 100%
Thrombocytopenia	3/4	£84.22	Cost of platelets transfusion
Febrile neutropenia	3/4	£1,337.42	HRG P23 multiplied by 100%
Anaemia	3/4	£930.04	HRG S06 multiplied by 50%
Fever/Infection	3/4	£1,103.37	HRG P05 multiplied by 50% plus medication[5]

Notes:

1. For mucositis/stomatitis/dysphagia grade 2, the expected value of the event is equal to 5% multiplied by the HRG cost plus 95% multiplied by the cost of benzydamine rinse.

2. For mucositis/stomatitis/dysphagia grade 3, the expected value of the event is equal to 10% multiplied by the HRG cost plus 90% multiplied by the cost of benzydamine rinse.
3. For nausea & vomiting grade 2, the expected value of the event is equal to 10% multiplied by the HRG cost plus 90% multiplied by the cost of 1st-line anti-emetic therapy for low emetogenic chemotherapy as per the North London Cancer Network guidelines (course of domperidone) for the duration of the event. See **Section 2.5** for adverse event durations.
4. For nausea & vomiting grade 3, the expected value of the event is equal to 30% multiplied by the HRG cost plus 70% multiplied by the cost of 1st-line anti-emetic therapy for low emetogenic chemotherapy as per the North London Cancer Network guidelines (course of domperidone) for the duration of the event. See **Section 2.5** for adverse event durations.
5. For fever/infection grade 3 or 4, the expected value of the event is equal to 50% multiplied by the HRG cost plus 50% multiplied by the cost of a course of anti-pyretic therapy.

Finally, there was significant overlap and/or duplication within the reporting of the adverse events. Following the process of isolating the events listed above, the dataset was further cleaned by removing duplicated/overlapping events that satisfied each of the following criteria:

- The events were assigned to the same patient; AND
- The events had the same COSTART term; AND
- The events had the same toxicity grade; AND
- The events had overlapping or matching onset dates

Following the elimination of overlapping and duplicated events, the final tally of patient events included in the analysis totalled 1,383 (678 in the RT group and 705 in the ERT group).

1.6 IMAGING

The economic model considers the costs of imaging scans performed, irrespective of when they occur. Information on the scans performed on the trial patients was not recorded in the dataset. Therefore UK clinical expert opinion was sought to provide estimates of the types of scans performed and their typical frequency for patients within this population. The UK Expert Panel indicated that on average scans may continue to be performed up to the 3rd year post-treatment, depending on individual circumstances. **Table 7** presents the findings of the expert panel, the unit costs of each type of scan and the costs applied to the economic model.

Table 7 Costs of imaging

Type and timing of scan	Number of scans	Proportion of patients	Unit cost[1]	Total cost applied to economic model
CT scan – staging	1	100%	£58.66	£58.66
MRI – staging	1	30%	£219.52	£65.86
CT scan – up to 1 year post-treatment	1	100%	£58.66	£58.66
CT scan – 1 to 2 years post-treatment	1	100%	£58.66	£58.66

CT scan – 2 to 3 years post-treatment	1	100%	£58.66	£58.66

Note:
1. The unit costs of CT scan and MRI are sourced from Reference Costs 2004.

The imaging costs are applied for each patient at the appropriate point in the model, provided that the patient has survived. Any costs incurred more than 1 year post-treatment are discounted at the appropriate rate for England and Wales (3.5%).

1.7 ROUTINE MONITORING

The economic model considers the costs of routine monitoring of patients performed by their specialist post-treatment and prior to progressive disease. Information on such health professional visits was not available from the trial dataset. Therefore local clinical expert opinion was sought to provide estimates of the frequency of specialist visits made by patients within this population. The UK Expert Panel indicated that routine monitoring of patients may continue up to the 4th year post-treatment, depending on individual circumstances. **Table 8** presents the findings of the expert panel, the unit cost of a visit and the costs applied to the economic model.

Table 8 Costs of routine monitoring

Timing of visit	Frequency	Unit cost[1]
Up to 5 weeks post-treatment	Weekly	£93.00
5 weeks to 1 year post-treatment	Monthly	
1 year to 2 years post-treatment	2-Monthly	
2 years to 4 years post-treatment	3-Monthly	

Note:
1. The unit costs of a specialist visit are sourced from Reference Costs 2004 (outpatient specialty code 800 – clinical oncology).

The visit unit cost is applied for each patient at the appropriate point in the model, provided that the patient has survived. Routine monitoring costs cease to be applied when patients move into progressive disease, where palliative/salvage care takes effect. Any costs incurred more than 1 year post-treatment are discounted at the appropriate rate for England and Wales (3.5%).

1.8 PROCEDURES

The economic model considers the costs of other procedures, in particular the percutaneous endoscopic gastronomy (PEG), which may be performed preventatively on patients within this population prior to the commencement of treatment. Information on such procedures was not available from the trial dataset. Local clinical expert opinion was sought to provide

estimates of the frequency of procedures received, and the UK Expert Panel indicated that a PEG would be inserted for approximately 10% of patients within this population receiving RT. The unit cost of the procedure was sourced from the 2004 Reference Costs (elective inpatient HRG F04, therapeutic endoscopic procedures) and was equal to £1,117.72.

The expected cost of PEG insertion (10% × £1,117.72 = £111.77) is applied for each patient in both treatment groups at the start of the model.

1.9 SALVAGE/PALLIATIVE CARE

The economic model assumes that the pattern of care changes after patients move into the progressive disease state. Information on palliative or salvage (secondary) therapy was recorded in the clinical trial by type of therapy. Unit costs were sourced for these results to arrive at estimates of cost of therapy (**Table 9)**.

Table 9 Costs of palliative/salvage care

Type of care	Proportion of patients (RT)	Proportion of patients (ERT)	Unit cost	Expected cost applied to model (RT)	Expected cost applied to model (ERT)	Proportion of patients reference
Community nursing - palliative/respite care	100%	100%	£428.55[1]	£428.55	£428.55	Assumption
Community nursing - cancer related	100%	100%	£289.43[1]	£289.43	£289.43	Assumption
Salvage surgery	12%	14%	£1,180.66[2]	£138.58	£162.27	Average from clinical study report for ITT population
Secondary radiotherapy	6%	6%	£2,699.99[3]	£150.25	£164.32	Average from clinical study report for ITT population
Secondary systemic therapy	21%	18%	£296.97[4]	£61.35	£52.08	Average from clinical study report for ITT population

Notes:

1. The unit costs of community nursing are sourced from Reference Costs 2004.
2. The unit cost of salvage surgery is sourced from Reference Costs 2004. It is equal to a weighted average of 3 elective inpatient HRGs (C54, C57 and C58: Mouth or Throat procedures). C54: unit cost £6,845.84, 1,194 procedures. C57: unit cost £2,063.40, 13,781 procedures. C58: unit cost £970.06, 89,882 procedures.
3. The unit cost of secondary radiotherapy is assumed to be the same as the standard cost of a course of once daily radiotherapy (**Table 2**).
4. The unit cost of secondary systemic therapy is assumed to be that of a standard cost of a course of cisplatin. Standard dose is 100 mg/m^2 and assuming an average body surface area of 1.88 m^2 yields a dose of 188 mg per cycle. Cost minimising vial choice based on prices from BNF 50 is: 1 × 100 mg vial (£50.22); 1 × 50 mg vial (£25.37); 4 × 10 mg vials (£5.85 each). Total is £98.99 per cycle, £296.97 for 3 cycles.

Clearly, the proportion of patients receiving the listed secondary therapies is limited by the follow-up of the clinical trial. Ideally, the economic model would require a proportion of all

patients who have progressed that received the various secondary therapies. Unfortunately, it was not possible to obtain those results and the ITT proportions are used as a proxy.

The costs are applied in the model for all patients at the point of progression. If that point occurs more than 1 year post-treatment, the costs are discounted at the appropriate rate for England and Wales (3.5%).

2 PATIENT OUTCOMES

Trial patients were allocated amongst eleven disease health states over the course of their actual or modelled (in the case of censored data) lifetime in order to evaluate their quality of life (QoL). The calculation of patient outcomes from the trial dataset was split into two distinct steps. Firstly, patients' QoL was assessed during the acute treatment phase with health states particular to the different adverse event statuses experienced by patients during treatment. Secondly, QoL during the post-treatment phase was assessed according to disease status.

2.1 OVERALL AND PROGRESSION-FREE SURVIVAL

Please refer to Technical Appendix 2 for a detailed description of the methods of the statistical cure model.

2.2 HEALTH STATE UTILITIES

Utility values for the health states were estimated from a study of oncology nurses in the UK using the EQ-5D. The objective of this study was to estimate utility values for a series of health states describing major side effects and post-treatment outcomes that may be experienced by patients undergoing treatment for stage III and IV head and neck cancer.

Seven health states described different grades of the acute toxicities, based on the National Cancer Institute (NCI) common toxicity criteria (CTC) for adverse events. Two further health states described late toxicities that may be experienced post-cessation of treatment. Two additional health states described possible final outcomes of treatment in terms of the success or failure of the treatment. Nursing staff from oncology centres around the UK were recruited for the study (n = 50), and screened to ensure they had suitable experience in patient care and therapy techniques to be able to act as patient proxies.

In the economic model the OS time for each patient was distributed amongst the eleven health states (**Table 10**).

Due to the volume of adverse events experienced by trial patients during the acute phase it was not possible to account for all the many possible combinations of adverse events that may affect patient QoL. Some simplifying assumptions were required to enable patient time during the acute phase to be allocated amongst the 7 in-treatment health states.

Table 10 Model health states and utilities

Health state	Definition	Utility
Acute phase health states		
A	General in–treatment – range of ≤ grade 1 adverse events	0.659
B	As health state A plus grade 3 or 4 mucositis, stomatitis and dysphagia	0.062
C	As health state A plus grade 2 mucositis, stomatitis and dysphagia	0.608
D	As health state A plus grade 3 or 4 nausea and vomiting	0.108
E	As health state A plus grade 2 nausea and vomiting	0.573
F	As health state A plus grade 3 or 4 acne and rash	0.226
G	As health state A plus grade 4 haematological toxicity	0.101
Post-acute phase health states		
H	Post treatment late toxicity: peripheral neuropathy	0.473
I	Post–treatment late toxicity: ototoxicity	0.657
J	Post–treatment loco–regional control	0.862
K	Post–treatment progressive or worsening disease	0.129

Firstly, it was assumed that patient QoL would be best represented by ranking the health states into a hierarchy with the worst health state (i.e. state B) taking precedence, followed by the second-worst (state G) and so on. Secondly, each patient's adverse events were consolidated to assess which health states they would, other things being equal, have spent time in and on how many occasions. Thirdly, using this gathered information on each patient utilities were assigned for the acute phase according to the following algorithm:

- If a patient experienced at least one health state B adverse event, then they were allocated the utility value for this health state for the average duration of this event multiplied by the number of events. Otherwise;
- If a patient experienced at least one health state G adverse event, then they were allocated the utility value for this state following the same rules. Otherwise;
- If a patient experienced at least one health state D adverse event, then they were allocated the utility value for this state following the same rules. Otherwise;
- If a patient experienced at least one health state F adverse event, then they were allocated the utility value for this state following the same rules. Otherwise;
- If a patient experienced at least one health state E adverse event, then they were allocated the utility value for this state following the same rules. Otherwise;

- If a patient experienced at least one health state C adverse event, then they were allocated the utility value for this state following the same rules. Otherwise;
- The patient is allocated the utility value for health state A for all remaining acute phase time.

This algorithm ensures a conservative approach to estimation of patient QoL during the treatment phase by allocating the worst possible utility score within the parameters of the modelled health states. The time within the acute phase and the average duration of each health state event is presented in **Table 11**.

Table 11 Acute phase time allocations

Parameter	Time (days)	Reference
Overall time in acute phase		
RT group (once daily)	49	Trial protocol
RT group (twice daily)	43	Trial protocol
RT group (concomitant boost)	42	Trial protocol
ERT group (all patients)	56	Trial protocol
Duration in health states		
Health state B	55.43	Average time in adverse event health states was calculated from all complete records of associated events in the trial dataset.
Health state C	34.46	
Health state D	13.14	
Health state E	29.82	
Health state F	72.92	
Health state G	44.32	

Clearly, the average durations in each health state may run past the allocated total time in the acute phase. So as not to bias the analysis, the full duration in the health state was applied where it caused the total time in the acute phase to overrun the allocated total. For example, if a once daily radiotherapy patient in the RT group experienced a health state B event, this would imply that the patient spends 55.43 days in health state B although only 49 days are allocated to this patient in the acute phase. The model would allow the full 55.43 days to be counted in health state B however no more acute phase adverse events are counted past that which causes the overlap into the post-acute phase. The overlapping time is subtracted from the patient's time allocation in the post-treatment phase. Conversely, if a patient died during the acute phase, then the time allocated to acute phase health states is capped by overall survival.

Following the acute phase, the remainder of each patient's overall survival duration is allocated between the post-treatment phase health states according to their associated progression free survival (health state J) and remaining survival with progressive disease (health state K). Health states H and I do not apply to patients in the primary comparison.