NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

MERCK PHARMACEUTICALS SINGLE TECHNOLOGY APPRAISAL SUBMISSION: ERBITUX® (CETUXIMAB) FOR THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD & NECK (LA SCCHN)

Contents

1 Background

1.1 Summary of decision problem

The purpose of this section is to summarise the decision problem and state the key factors that are addressed in the submission:

1. **intervention**

The licensed indication is: Erbitux (cetuximab) plus radiotherapy (ERT) for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck. We advocate the use of cetuximab in those patients who are considered inappropriate for chemoradiotherapy but suitable for radiotherapy. The combination of radiotherapy and cetuximab should be given in accordance with the marketing authorisation, as described in the cetuximab SPC.

2. **population, including subgroups**

Patients eligible for cetuximab plus radiotherapy treatment are those with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). The pivotal trial, Bonner et al, 2006[1] (EMR62-202-006) upon which the licence was granted included patients with SCCHN subtypes oropharynx, hypopharynx and larynx.

3. **relevant comparator(s)**

Radiotherapy alone.

4. **outcomes**

The primary outcome was duration of locoregional control; secondary outcomes included overall survival, progression free survival and safety. Additionally, disease-specific Quality of Life instruments (EQ5D, QLQC-30 with Head & Neck module) were used to collect quality of life data.

Outcomes:

Variable/ statistic	RT alone (N=213)	ERT (N=211)	Treatment comparison	
			p-value	Hazard ratio (95%CI)
Locoregional control Median duration (months)	**14.9**	**24.4**	0.005	0.68 (0.52-0.89)
Rate at 2 years (%)	**41**	**50**		
Overall Survival Median duration (months)	**29.3**	**49.0**	0.03	0.74 (0.57- 0.97)
Rate at 3 years (%)	**45**	**55**		
Progression-free survival Median duration (months)	**12.4**	**17.1**	0.006	0.70 (0.54-0.90)
Rate at 2 years (%)	**37**	**46**		

ERT = Erbitux + radiotherapy

Common adverse events (all grades ≥30%) of subjects in either group from the pivotal trial (Bonner et al, 2006) were as follows;

Adverse event	RT		ERT		p value#	
	n=212		n=208			
	All grades	Grades 3-5	All Grades	Grades 3-5	All Grades	Grades 3-5
	% of patients					
Mucositis	94	52	93	56	0.84	0.44
Acneform rash	10	1	87	17	<0.001	<0.001
Radiation dermatitis	90	18	86	23	0.24	0.27
Weight loss	72	7	84	11	0.005	0.12
Dry mouth	71	3	72	5	0.83	0.32
Dysphagia	63	30	65	26	0.68	0.45
Asthenia	49	5	56	4	0.17	0.64
Nausea	37	2	49	2	0.02	1.00
Constipation	30	5	35	5	0.35	1.00

# p values were determined with the use of a Fisher's exact test
ERT = Erbitux + radiotherapy

Key Benefits

A fixed course of treatment (maximum of 8 weeks) of cetuximab plus radiotherapy resulted in clinically meaningful benefits over radiotherapy alone:

- Improved median duration of locoregional control by 9.5 months (from 14.9 months (RT) to 24.4 months (ERT) (p=0.005)).

- Prolonged median overall survival by 19.7 months (from 29.3 months (RT) to 49.0 months (ERT) (p=0.03)) with a 26% reduction in the risk of death.
- Significantly improved progression-free survival, with a median of 17.1 months compared to 12.4 months in those patients treated with radiotherapy alone (p=0.006).
- When used in combination with radiotherapy, cetuximab does not significantly exacerbate the toxicities associated with radiotherapy.

5. **key issues**

There are no set treatment guidelines for patients with locally advanced SCCHN.[2] Although current clinical opinion supports the emergence of chemoradiotherapy as a preferred treatment option, in the UK, radiotherapy alone is still the treatment offered to this group of patients in 39% of cases[3]. The value of chemoradiotherapy is, however, counterbalanced by increased and often prohibitive toxicity[4, 5]

Epidermal Growth Factor Receptor (EGFR) is abnormally activated in epithelial cancers, including head & neck cancer. Almost all such neoplasms express high levels of EGFR, a feature associated with poor clinical outcome [6, 7]. Radiation increases the expression of EGFR in cancer cells and blockade of EGFR signalling sensitises cells to the effects of radiation.[8]

Cetuximab is an IgG1 monoclonal antibody directed against the EGFR receptor and enhances the cytotoxic effects of radiation in squamous cell carcinoma.[9]

Cetuximab plus radiotherapy is therefore proposed as a treatment option for those patients with LA SCCHN who would normally receive radiotherapy alone.

1.2 Description of technology under assessment

6. **Give the brand name, approved name and where appropriate, therapeutic class.**

Brand name: Erbitux

Approved name: cetuximab

Therapeutic class: Antineoplastic agents, monoclonal antibody.

7. **Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If yes, please give the date it received it. If no, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).**

UK marketing authorisation for cetuximab plus radiotherapy for the treatment of LA SCCHN was received on March 31st 2006.

8. **Does the technology have regulatory approval outside of the UK?**

Yes. Dates of regulatory approvals and indications are tabled below:

Territory	Licensed indication(s)	Date of approval
European Union (EMEA)	• Cetuximab + radiotherapy for locally advanced SCCHN	March 31st 2006
USA (FDA)	• Cetuximab + radiotherapy for locoregionally advanced SCCHN • Cetuximab monotherapy for recurrent or metastatic disease where prior platinum-based therapy has failed	March 1st 2006
Cetuximab has received marketing authorisation for SCCHN in 25 EU countries and 7 countries outside of the EU.		

9. **If the technology has not been launched, please supply the anticipated launch date for the UK.**

Not applicable: the technology has been launched

10. **Is the technology subject to any other form of Health Technology Assessment either in the UK or elsewhere? If so, what is the timescale for completion?**

Yes.

The Scottish Medicines Consortium (SMC) approval for the use of cetuximab + radiotherapy was received on June 9th 2006 and became public on July 10th 2006.

The SMC detailed advice is available at:
http://www.scottishmedicines.org.uk/

The SMC recommendation stated the following:

"Cetuximab (Erbitux®) is accepted for restricted use within NHS Scotland in combination with radiation therapy for the treatment of patients with locally advanced squamous cell carcinoma of the head & neck.

It is restricted to patients who are not appropriate for, or unable to tolerate, chemoradiotherapy and who are of good performance status with no evidence of distant metastases. It is also restricted to use by specialists in the management of head and neck cancer"

The London Cancer New Drugs Group (LCNDG) issued a briefing on May 24th 2006 supporting a role for cetuximab in patients inappropriate for chemoradiotherapy, who currently receive radiotherapy alone. (http://www.nelm.nhs.uk/Record%20Viewing/viewRecord.aspx?id=565502).

We are not aware of any formal Health Technology Assessments planned or ongoing outside of the UK.

11. **What is the principal mechanism of action of the technology?**

Epidermal Growth Factor Receptor (EGFR) is abnormally activated in epithelial cancers, including head & neck cancer. Almost all such neoplasms express high levels of EGFR, a feature associated with poor clinical outcome [6, 7]. Radiation increases the expression of EGFR in cancer cells and blockade of EGFR signalling sensitises cells to the effects of radiation.[8]

Cetuximab is an IgG1 monoclonal antibody directed against the EGFR receptor and enhances the cytotoxic effects of radiation in squamous cell carcinoma.[9]

Cetuximab binds to the EGFR receptor, blocking EGFR signalling and thus enhancing the cytotoxic effects of radiation in squamous cell carcinomas.[9] Additional effects of EGFR blockade by cetuximab are: inhibition of cancer cell growth, metastatic spread and angiogenesis, induction of apoptosis – all leading to cancer cell death.[10]

12. **For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained release tablet), strength(s) and pack size(s) will be available?**

Formulation: ready-to-use solution for intraveneous administration
Strength: 100mg cetuximab per 50mL vial (2mg/mL)
Pack size: vials are individually packed.

13. **What is the acquisition cost of the technology (minus VAT)? If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs. For devices, provide the list price and average selling price.**

One 50mL vial of cetuximab costs £136.50 (Source BNF: March 2006)

14. **What are the (proposed) main indications?**

The **licensed** indication is: Erbitux (cetuximab) plus radiotherapy for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

The ***proposed*** use in the UK is: Erbitux (cetuximab) plus radiotherapy for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck for whom chemoradiotherapy is not considered an appropriate option.

15. **What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.**

Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Cetuximab (mg/m^2)	400	250	250	250	250	250	250	250
Radiotherapy* (Gys/week)		10	10	10	10	10	10	10

*The length of course, total dose and schedule of radiotherapy depends upon the locally accepted protocol in use at each hospital. The scheme above depicts a typical radiotherapy schedule received by patients in the pivotal trial. Radiotherapy is usually delivered daily.

The following applies to the cetuximab therapy only:

Course of treatment:
It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab therapy until the end of the radiation therapy period (usually 7 to 8 weeks).

Dose: as indicated in the table above.

Dose frequency: once a week

Repeat course of treatment: none

16. **What other therapies, if any, are likely to be prescribed as part of a course of treatment?**

The following therapies are specified in the Summary of Product Characteristics to be administered with cetuximab therapy:

Premedication: Prior to the first infusion, patients must receive premedication with an antihistamine. This premedication is recommended prior to all subsequent infusions.

Some centres may use treatments such as topical antibiotics and/or oral tetracyclines to relieve the symptoms of the acneform rash which is the most common side effect of cetuximab.

17. **For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? If yes, provide details.**

Administration requirements: cetuximab is given as a weekly infusion in an out-patient / day-case setting.

Monitoring requirements: Severe infusion-related reactions (hypersensitivity reactions) have been reported. It is therefore recommended that patients are premedicated and should be observed during and for one hour after the completion of cetuximab therapy for any signs of infusion-related reactions.

18. **For pharmaceuticals, please provide a Summary of Product Characteristics (SPC) or draft SPC as an appendix to the submission.**

The SPC is attached as a pdf file.

19. **For devices, please provide the (anticipated) CE marking, including the indication for use, (draft) technical manual and details of any different versions of the same device, as an appendix to the submission.**

Not applicable

20. **What is the current usage of the technology in the NHS? Include details of use in ongoing clinical trials.**

There are no trials with cetuximab in SCCHN currently recruiting in the UK. A trial in the recurrent / metastatic setting (EXTREME) has finished recruiting and is currently in the follow-up phase. Centres in Scotland are planning to participate in RTOG-0522 (a study being run by an American cooperative group) but have not yet commenced recruitment. Neither of these trials explore the use of cetuximab in the licensed / proposed setting in the UK. We are unable to accurately assess the number of NHS patients who have received cetuximab treatment specifically for head & neck cancer since the marketing authorisation was only granted in March 2006.

1.3 Context

21. **Please provide a brief overview of the disease and current treatment options.**

Squamous cell carcinoma of the head and neck (SCCHN), also generally referred to as head and neck cancer, is the generic term used for a heterogeneous group of malignant tumours. This term includes over 30 specific sites (ICD10 codes) of cancer; each particular site is relatively uncommon. The majority of these cancers arise from the surface layers of the upper aerodigestive tract: the mouth, lip and tongue (oral cavity), the upper part of the throat and respiratory system (pharynx), and the voice-box (larynx). Other less common sites include the salivary glands, nose, sinuses and

middle ear. Cancer which originates in the nerves and bones of the head and neck are very rare.[11]

In the UK, head and neck cancer is one of the top ten most commonly diagnosed cancers and accounts for more than 7,800 new cases each year[12]. The incidence of head and neck cancer, including cancer of the mouth, in the UK has risen by one quarter over the past 10 years[13]. Tobacco and alcohol consumption are aetiological factors involved in the onset of SCCHN, which commonly affects middle-aged or older men.[2] Incidence is associated with exposure to risk factors, and there are pronounced geographical variations[14]. SCCHN tends to be a disease of deprivation and of men.[15] The risk of men developing the disease is four times greater for men living in the most deprived areas[16].

Around 90% of head and neck cancers are squamous cell carcinomas[17]. Approximately 50% of patients have locally advanced SCCHN[14]. The table below gives the T, N, M staging system for head and neck cancers. Patients classified as having locally advanced disease are those with stages III, IVA and IVB, as shaded in the table below.

Stages of SCHNN

Stage	T stage	N stage	M stage	Historic 5 year survival	Treatment goal	% of cases
0	Tis	N0	M0	NA	Curative	30-40%
I	T1	N0	M0	56-68.1%		
II	T2	N0	M0	45.4- 52.9%		
III	T3 T1-3	N0 N1	M0 M0	36.3 -56.3%	Curative	> 50%
IV A	T4a T1-4a	N0 or 1 N2	M0 M0	26.5- 38.9%		
IV B	T4b Any T	Any N N3	M0 M0			
IV C	Any T	Any N	M1	NA	Palliative	10%

Source: Adapted from an article by Seiwert et al (2005) who acknowledge the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, Inc.
5-Year survival, historically 1985 – 1991, rates vary depending on anatomic site of tumour
NA: not available/or applicable

EGFR is expressed in nearly all SCCHN tumours [1,18].

Radiotherapy has evolved as the mainstay of treatment for locoregionally advanced SCCHN. Additional benefit can be obtained with accelerated fractionation by concomitant boost radiotherapy (reduction in overall treatment time, with or without change in fraction size and total dose)[19] or hyperfractionation (multiple smaller dose fractions (<2 Gy) delivered over the same time as conventional RT). [20]

An evolving standard is radiotherapy used in combination with chemotherapy (CRT). Cisplatin 100mg/m^2 every 3 weeks is the most commonly used chemotherapy in CRT treatment. Although studies[21],[22] have shown CRT can improve survival rates and local control compared to RT alone, this improvement comes at the expense of acute toxicity[4,5]. Consequently, poor tolerance has been reported in up to 1/3 of cases, especially in patients receiving high-dose treatments[23]

22. **What was the rationale for the development of the new technology?**

Anti-cancer drugs with molecular targets offer an interesting treatment approach because of their specificity. There was an expectation amongst researchers that the new generation of drugs would be very active and generally well tolerated. Erbitux is a monoclonal antibody, which specifically targets EGFR. Epidermal Growth Factor Receptor (EGFR) is abnormally activated in epithelial cancers, including head & neck cancer. Almost all such neoplasms express high levels of EGFR, a feature associated with poor clinical outcome[6, 7]. Radiation increases the expression of EGFR in cancer cells and blockade of EGFR signalling sensitises cells to the effects of radiation [8].

In pre-clinical models, Erbitux showed synergistic activity with RT, leading to early phase trials to assess this combination [9] . These promising results led to the pivotal Phase III trial (Bonner et al) being designed and conducted.

23. **What is the suggested place in therapy for this technology with respect to treatments currently available?**

Cetuximab + radiotherapy is expected to be used in patients with locally advanced SCCHN who would otherwise receive radiotherapy alone. It is not expected to replace chemoradiotherapy treatment.

24. **Describe any current variation in services and/or uncertainty about best practice, including cost effectiveness.**

Radiotherapy regimens differ from centre to centre in the UK depending upon capacity, expertise and clinical / patient preference. Although hyperfractionated and / or concomitant boost radiotherapy schedules give a better clinical outcome [24] not all centres in the UK are currently able to deliver such schedules.

Whilst chemoradiotherapy is evolving as a standard in LA SCCHN treatment, only about 40% of patients in the UK currently receive such treatment[3]. Reasons may include: contraindications, toxicity, doctor and patient preference.

To our knowledge, there have been no comparative Health economic evaluations between RT and CRT conducted.

25. **Provide details of any relevant guidelines or protocols.**

NICE issued Guidelines in the Treatment of Head & Neck Cancer in 2004.[11]

SMC issued its positive advice for the use of cetuximab in LA SCCHN in combination with RT on July 10th 2006.

1.4 Comparator(s)

26. **Describe the relevant comparator(s) and provide a justification for your selection. In some cases, comparisons with more than one comparator or combination-therapy comparators will be necessary. The Institute considers the most relevant comparators to be those that the new technology is attempting to displace from UK practice.**

Radiotherapy alone is the only comparator to cetuximab + radiotherapy since this is where the proposed use lies, supported by the clinical evidence and the marketing authorisation.

27. **What are the main differences in the indications, contraindications, cautions, warnings and adverse effects between the proposed technology and the main comparator(s)?**

In this setting cetuximab + radiotherapy share the same indication as radiotherapy alone. The only additional contraindication to receiving cetuximab is hypersensitivity to any of the ingredients in cetuximab. The cautions, warnings and adverse events to cetuximab are listed in full in the SPC and briefly below:

Special warnings and precautions for use: infusion-related reactions, respiratory disorders, skin reactions, special populations.

Adverse effects in combination with radiotherapy were those typical of radiation therapy (mucositis, radiation dermatitis, dysphagia, leucopenia). In the pivotal study reporting rates of severe acute radiation dermatitis and mucositis as well as late radiation therapy-related events were slightly higher in patients receiving radiotherapy + cetuximab than radiotherapy alone.

Cetuximab specific side effects include: hypomagnesemia, conjunctivitis, dyspnoea, increased liver enzymes, skin reactions and skin lesions, infusion-related reactions (mild, moderate & severe).

2 Clinical evidence

2.1 Identification of studies

28. **Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided.**

Rigorous electronic literature searches were conducted using publicly available and company-specific databases to identify randomised controlled trials of the use of cetuximab in locally advanced SCCHN.

29. **the specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***The Cochrane Library***

Datastar Web (www.datastarweb.com) was used to search Medline and Embase.
The Cochrane library was accessed via the National electronic library for Health. (www. http://www.nelh.nhs.uk/cochrane.asp).
The ASCO (American society of clinical oncology) website was searched at www.asco.org.

30. **the date the search was conducted**

Medline 1993 to date and Medline in process were searched (latest 8 weeks) on 24 July 2006.

The Cochrane library was searched on 21st July 2006.

Embase 1993 to date and Embase alert were searched on 24 July 2006.

31. **the date span of the search**

Medline and Embase were searched from 1993 to date including the last 8 weeks. The ASCO website was searched from 1995 to 2006.The Cochrane library was searched from 1993 to 2006.

32. **the complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)**

Medline 1993 onwards:
Advanced search option chosen.
Free text search on cetuximab OR Erbitux ('OR' being the Boolean term).
MeSH search of Head and neck neoplasms
Search terms 1 and 2 combined using the Boolean term 'AND'.
All restricted to articles relating to clinical trials, humans and in English.
Further restricted using the inclusion and exclusion criteria as listed in response to question 34.

Medline – In Process –latest 8 weeks:
Advanced search option chosen.
Free text search on cetuximab OR Erbitux ('OR' being the Boolean term).
MeSH search of Head and neck neoplasms
Search terms 1 and 2 combined using the Boolean term 'AND'.
All restricted to articles relating to clinical trials, humans and in English.
Further restricted using the inclusion and exclusion criteria as listed in response to question 34.

Embase 1993 onwards
Advanced search option chosen.
Free text search of cetuximab OR Erbitux ('OR' being the Boolean term).
Head and neck cancer used as the major descriptor term
Search terms 1 and 2 combined using the Boolean term 'AND'.
All restricted to articles relating to clinical trials, humans and in English.

Further restricted using the inclusion and exclusion criteria listed in response to question 34.

For Embase Alert latest 8 weeks:
Advanced search option chosen.
Free text search on cetuximab.
Head and neck cancer used as the major descriptor term
Search terms 1 and 2 combined using the Boolean term 'AND'.
All restricted to articles relating to clinical trials, humans and in English.
Further restricted using the inclusion and exclusion criteria as listed in response to question 34.

The Cochrane Library:
Searched via the Cochrane website available via the national electronic library for health.
Then searched on the Cochrane Library advanced search option.
Search carried out on: ALL Cochrane Library and ALL records.
Free text search on "cetuximab" and Search All Text.
Further restricted using the inclusion and exclusion criteria as listed in response to question 34.

The ASCO website:
Meetings & Education chosen. Then Abstracts chosen.
Advanced search option chosen.
Free text search on cetuximab AND head and neck (AND as the Boolean term).
Further restricted using the inclusion and exclusion criteria as listed in response to question 34.

33. **details of any additional searches, for example searches of company databases (include a description of each database)**

Oncomed (a Merck global internal database of oncology materials and publications) was searched, however, no additional information was found over and above that which was publicly available. In addition, Medisi (a Merck global clinical document database) was searched for relevant clinical study reports.

34. **the inclusion and exclusion criteria**

Inclusion Criteria

Published papers or abstracts which evaluated the following were included in the search:

Cetuximab or Erbitux had to be the major focus of the article in order to eliminate those which only mentioned cetuximab as part of a discussion on treatments in head and neck cancer.

Clinical trial data publications – to ensure that current data from clinical trials was accessed (as opposed to reviews of clinical trials).

Where applicable in the search engine only trials in English and in humans were selected.

Exclusion Criteria

Published papers or abstracts which evaluated the following were excluded from the search:

Studies which were not randomised controlled trials.

Reviews of head and neck cancer, head and neck clinical trials or ongoing clinical trials and future developments – excluded as only actual reported clinical trial data was required.

Studies which were not related to cetuximab.

35. **the data abstraction strategy.**

The search terms as previously described were entered into the database being searched. The terms were then combined as previously described. The titles and abstracts of all papers revealed at this stage were then reviewed and eliminated manually if they were not relevant to the search – as per the inclusion and exclusion criteria. All relevant papers revealed via this search were then used in this application.

2.2 Study selection

2.2.1 Complete RCT list

36. **Provide a list of all RCTs that compare the intervention with other therapies, including placebo. The list must be complete and will be validated by searches conducted by the assessors.**

Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

To date, two phase III, RCTs of cetuximab in SCCHN have been completed. In addition, there have been a number of phase I & II, single-arm, uncontrolled studies of cetuximab in this tumour type.

The RCTs are:

Bonner JA, Harari PM, Giralt J, et al
Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.
N Engl J Med. 2006;354(6):567-78.

Burtness B, Goldwasser MA, Flood W, et al
Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study.

J Clin Oncol. 2005;23(34):8646-54

2.2.2 Relevant RCT list

37. **List all randomised trials that compare the technology directly with the main comparator(s). If there are none, state this.**

Where data from a single study have been drawn from more than one source (e.g. a poster and a published report) and/or where trials are linked (e.g. an open-label extension to an RCT), this should be made clear.

Bonner JA, Harari PM, Giralt J, et al
Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.
N Engl J Med. 2006;354(6):567-78.

This is the only RCT completed that examines the use of cetuximab in combination with radiotherapy in the treatment of locally advanced SCCHN.

38. **Please provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 6–12 months.**

No ongoing studies are examining the use of cetuximab in combination with radiotherapy in the treatment of locally advanced SCCHN. The only ongoing studies of cetuximab are examining the use of Cetuximab in combination with chemotherapy in recurrent / metastatic SCCHN.

39. **A flow diagram of numbers of studies included and excluded at each stage should be provided as per the QUORUM statement**

Publications identified Potentially relevant studies identified and screened for retrieval (n=175)	
Medline 1993 to date	23
Medline in process	0
Embase 1993 to date	138
Embase Alert	0
ASCO 1995 to date	14
Cochrane library	0

↓

Publications excluded based on title abstract	
No suitable outcomes eg an ongoing study or non-controlled trials	20
Review article or comment	140
Not a cetuximab study	10

↓

Publications excluded based on full publication	
Duplicates	2
Review article	1
RCT not in the correct setting	1

↓

Trials included in systematic review, n = 1

2.3 Summary details of RCTs

40. **As a minimum, the summary should include information on the following aspects of the study but the list is not exhaustive. Where there is more than one RCT please tabulate the information.**

2.3.1 Methods

41. **Describe the trial design (e.g. degree and method of blinding and randomisation) and interventions.**

Bonner et al. Radiotherapy plus cetuximab for Squamous-Cell Carcinoma of the Head & Neck.

This study examined the efficacy and safety of cetuximab plus radiotherapy in LA SCCHN compared with radiotherapy alone in patients who were radiotherapy naïve for SCCHN and had not had prior chemotherapy within the previous 3 years. This was a randomised, open-label, phase III, comparative study with a blinded review of tumour imaging data by an independent expert review committee. The primary end-point was the duration of locoregional control.

Patients with stage III or IV (locally advanced), non metastatic squamous-cell carcinoma of the oropharynx, hypopharynx or larynx were recruited from 73 centres in 15 countries. Recruitment ran from April 1999 until March 2002.

The study was conducted in accordance with ICH-GCP.

All patients underwent an initial screening phase in the two weeks before the start of treatment. This included a comprehensive examination of the head and neck area, including panendoscopy and CT or MRI imaging. A chest radiograph was also obtained.

Before registering a patient into the study, investigators selected one of three radiotherapy regimens; a traditional once daily regimen, a hyperfractionated, twice daily regimen or a concomitant boost regimen (see Table 1).

Table 1. Radiotherapy regimen options (Bonner et al, 2006)

Regimen	Total radiation dose	Once-daily fractions	Twice-daily fractions
Once-daily	70.0 Gy in 35 fractions	2.0 Gy/fraction; 5 fractions/week for 7 weeks	Not applicable
Twice-daily	72.0-76.8 Gy in 60-64 fractions	Not applicable	1.2 Gy/fraction; 10 fractions/week for 6.0-6.5 weeks
Concomitant boost	72.0 Gy in 42 fractions	32.4 Gy; 1.8 Gy/fraction; 5 fractions/week for 3.6 weeks	Morning dose: 21.6 Gy; 1.8 Gy/fraction; 5 fractions/week for 2.4 weeks Afternoon dose: 18.0 Gy; 1.5 Gy/fraction; 5 fractions/week for 2.4 weeks

Patients were randomised in a 1:1 ratio to either radiotherapy alone or to radiotherapy plus cetuximab. Randomisation used a minimisation method, stratifying patients by:

- Karnofsky Performance Status (60-80 vs 90-100)
- Nodal stage (N0 vs N+)
- Tumour stage (T1-T3 vs T4)
- Radiotherapy regimen (once-daily, twice daily or concomitant boost).

This was to ensure even distribution of patients between the two treatment groups on these important prognostic indicators.

Patients assigned to the combination treatment arm received an initial loading dose of cetuximab (400mg/m^2) in week one followed by a weekly maintenance infusion of 250mg/m^2 in weeks 2-8. Radiotherapy commenced in week 2 in this treatment arm.
Table 2, provides an overview of the study treatment schedule and Table 3 the overall study schedule.

Table 2. Treatment Schedule

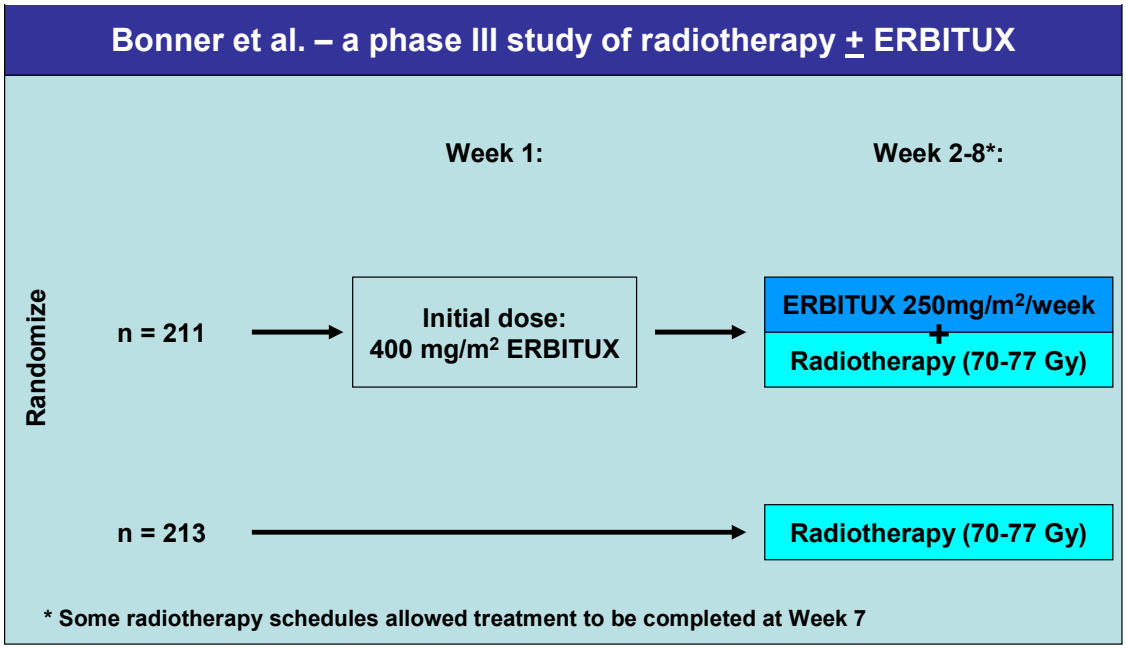


Table 3. Study Schedule.

			Post-treatment		5-year follow-up period	
Study procedures	**Pre-treatment**	**Treatment**	**4 Weeks**	**8 Weeks**	**Years 1 and 2 Every 4 Months**	**Years 3 to 5 Every 6 Months**
Informed consent	X					
Medical history	X					
Screening tests	X[1]					
Dental evaluation	X					
Lesions/nodes diagrams	X					
Gastrostomy placement (recommended)	X					
Urinalysis	X					
Pharmacological profile	X	X[2]		X		
Hematology/ chemistry profile	X	weekly	X	X	X[3]	
QoL questionnaire (QLQ)C30/H&N35	X	X[4]		X	X[4]	
Physical examination	X	X	X[5]	X	X	X
Neck dissection	X (plan)		X[6]	X[6]		
Tumor assessment	X (biopsy)		X	X	X	X
Imaging assessments	X			X	X	X
RTQA review		X[7]		X		
EGFR assessment		X[8]				
Adverse events		Continuous documentation of all AEs			Follow-up of cetuximab related AEs to resolution	
Radiotherapy ± Cetuximab		X				

1 Screening tests included an electrocardiogram (ECG) and chest X-ray. A beta human chorionic gonadotropin (ß-HCG) pregnancy test was performed within 7 days of the start of therapy for females of childbearing potential. If clinically indicated, hepatitis B surface antigen, hepatitis C, and human immunodeficiency virus (HIV) testing were performed.
2 Pharmacologic samples (for HACA and pharmacokinetic [PK] analysis) were collected before the final cetuximab infusion, regardless of cetuximab dosing delays, for all subjects treated with RT + cetuximab
3 Haematology and chemistry profiles were only performed during year 1 of follow-up.
4 QLQ-C30/H&N35 was completed at randomization, before starting the fourth week of RT, 8 weeks following the completion of RT, and at the next two 4-month follow-up evaluations.
5 Additionally, an AE assessment by the investigator or an off-site well-being assessment was required.
6 It was recommended that the planned post-RT neck dissection be performed 4 to 8 weeks after the completion of RT. For subjects who underwent the neck dissection before the 8-week post-treatment evaluations, all imaging assessments were to be performed before the scheduled neck dissection.
7 Rapid RT quality assurance begun as initial simulation films were submitted within 5 working days of the simulation and before the start of treatment.
8 Subjects could have begun the study without the EGFR results; however, tumour tissue was to be sent for assessment within 2 weeks of randomization.

2.3.2 Population

42. **Provide details of the inclusion and exclusion criteria and describe the patient characteristics at baseline. Highlight any differences between study groups.**

The main inclusion criteria were:

- Stage III/IV LA SCCHN of the oropharnyx, hypopharnyx or larynx, with an expected survival of ≥ 12 months
- No evidence of distant metastases.
- Measurable disease
- Medically suitable for definitive RT therapy.
- Karnofsky performance status of at least 60
- Neutrophils ≥1.5 x 10^9/L; platelets ≥100 x 10^{12}/L; bilirubin ≤25μM/L; alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) ≤ 2 x the upper limit of normal; serum creatinine ≤ 133μM/L or estimated creatinine clearance ≥ 50 mL/min; normal serum calcium.

The main exclusion criteria were:

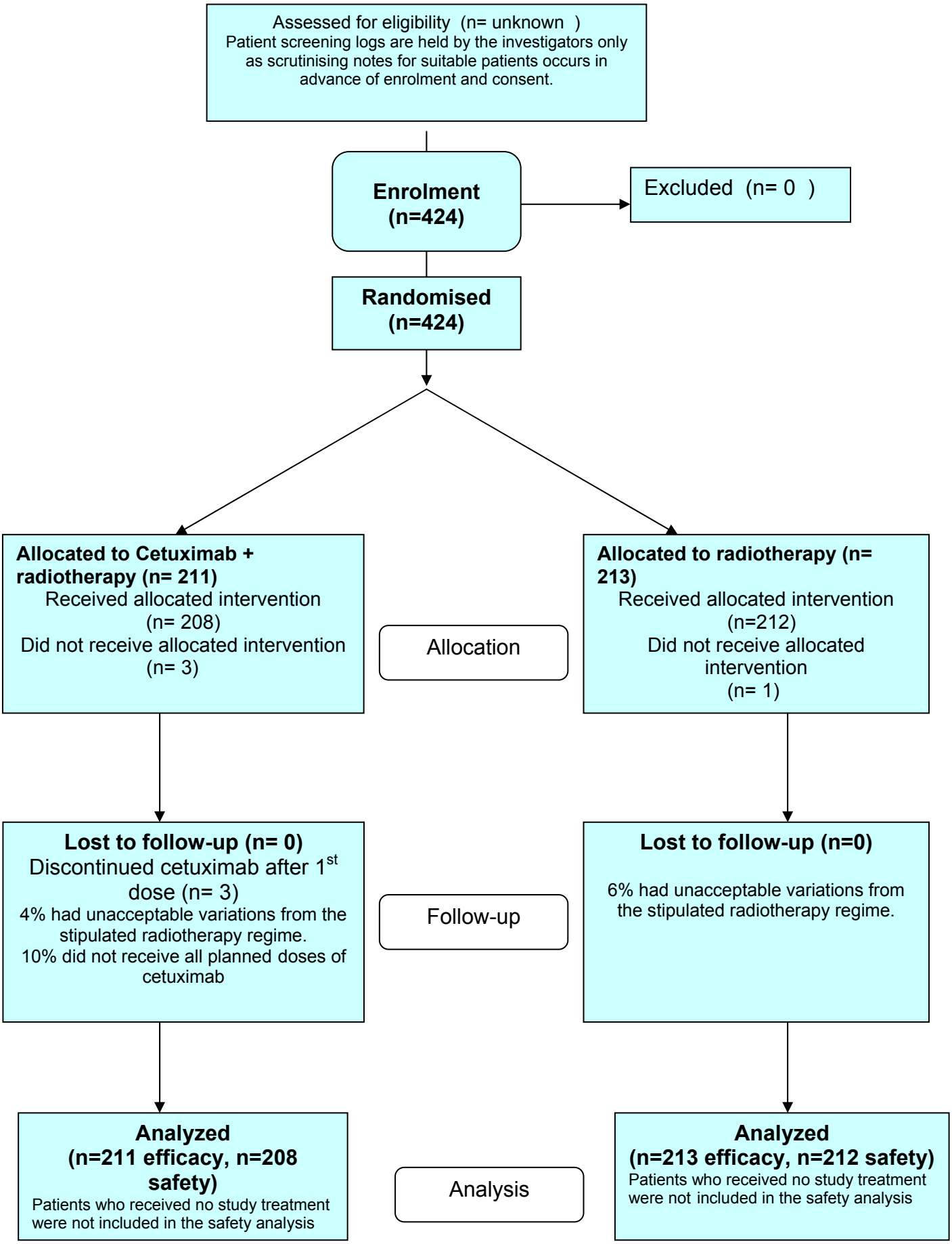
- A history of a previous cancer
- Chemotherapy within the previous three years
- Prior radiotherapy or surgery for head & neck cancer.

EGFR-expression was not an inclusion criterion in this trial. However, EGFR-expression was analysed in the majority of patients enrolled in the trial. EGFR over–expressing cells were found in >99% of patients tested.

2.3.3 Patient numbers

43. **Provide details of the numbers of patients eligible to enter the trial, randomised, and allocated to each treatment. Provide details of patients who crossed over treatment groups and dropped out from the trial. This information should be presented as a CONSORT flow chart.**

Flowchart of Patients in Study -Bonner NEJM 2006



2.3.4 Outcomes

44. **Provide details of the outcomes investigated and the measures used to investigate those outcomes. This may include therapeutic outcomes and patient-related outcomes such as assessment of quality of life, social outcomes etc. and any arrangements to measure concordance. Where appropriate, also provide details of the principal outcome measure(s) including details of length of follow-up, timing of assessments, scoring methods, evidence of validity and current status of the measure (e.g. approval by professional bodies, licensing authority, etc.).**

The primary objective of this study was to examine the duration of locoregional control (LRC) of the patients' tumours.
Secondary endpoints included overall survival (OS), progression free survival (PFS), response rate (RR), safety and quality of life (QoL).

LRC and RR were assessed using serial CT or MRI imaging of the tumour site. The assessments were made by an independent review committee made up of experts in the field. They performed this assessment according to a predefined written protocol and were blind to patients' treatment allocation.

The duration of LRC was defined as the time from the date of randomisation until the first documented progression, recurrence of locoregional disease or until death from any cause.

A complete response was defined as no remaining detectable disease. A partial response corresponded to a reduction of 50% or more in the sum of all the bidimensional products of the measurements of all lesions. Disease progression was defined as a 25% or greater increase in the sum of all the bidimensional products of the measurements of all lesions. Stable disease was defined as no change in tumour dimensions that was sufficient to equate to either disease progression or a partial response.

Survival data and safety data were collected in patients' study records (case record forms) at regular study visits, other patient contacts or by tracing events where these were managed at institutions other than the investigator site. Overall survival was calculated as the time from randomisation until death from any cause. Progression free survival was calculated from the date of randomisation until the first documented locoregional or distant progression or death from any cause.

QoL data were assessed using the EORTC QLQ-C30 (version 3.0) and QLQ-H&N35 instruments. The QLQ-C30 is a cancer specific self-administered multi-dimensional core questionnaire. Fifteen scales were derived from the initial 30 items: five functional scales, three symptom scales, six symptom single item scales and one global health status\QoL scale.
The QLQ-H&N35 is a head and neck cancer specific module, which is administered in conjunction with the QLQ-C30 questionnaire. Eighteen scales were derived from the initial 35 items: seven multi-item symptom scales and eleven single-item symptom scales.
The scores were calculated in accordance with the scoring procedure defined in the EORTC Scoring Manual.[25]

Patients were followed up until death or until the data cut off point as predefined in the study protocol and driven by the primary event rate. Median follow-up was 54.0 months.

This study was submitted to the EMEA as the main trial supporting a licence application for the use of cetuximab in combination with radiotherapy for the treatment of locally advanced head and neck cancer. In March 2006 the EMEA granted a marketing authorisation for the indication "In patients with locally advanced squamous cell cancer of the head and neck, cetuximab is used concomitantly with radiation therapy. It is recommended to start cetuximab therapy one week before radiation therapy and to continue cetuximab until the end of the radiation therapy period."

2.3.5 Statistical analysis and definition of study groups

45. **State the primary hypothesis or hypotheses under consideration and statistical analysis used in testing hypotheses. Also provide details of the power of the study and a description of sample size calculation including assumptions. Provide details of how the analysis took account of patients who withdrew (e.g. a description of the intention-to treat analysis including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken.**

End Points

The primary objective of this study was to examine the duration of locoregional control (LRC) of the patients' tumours.
Secondary endpoints included overall survival (OS), progression free survival (PFS), response rate (RR), safety and quality of life (QoL).

Power Calculations

Assuming an 18-month enrolment period and a minimum follow-up of 12 months, a sample of 208 subjects per group was calculated to provide 90% power to detect a difference in the duration of locoregional control at the 5% significance level.

Statistical Methods

Efficacy:

Distributions of time-to-event variables were estimated using the Kaplan-Meier product-limit method. Treatment effects were compared with the use of a stratified log-rank test and the three-year rates were compared between treatment groups with the use of a z-test. The cox regression method was used to estimate the hazard ratios and their 95% confidence intervals. Response rates were compared between treatment groups with use of Cochran-Mantel-Haenzel test. Analyses were performed on the intention to treat population.

Safety:

This was analysed using descriptive statistics based upon the “as-treated population” which comprised all subjects who received at least one dose of cetuximab or one fraction of radiotherapy.

2.4 Critical appraisal

For each of the following methodological topics, choose the description that best fits each trial. If there is more than one trial, tabulate the responses, highlighting any ‘commercial in confidence’ data. Your results will be validated by the assessor.

2.4.1 Randomisation

46. **Which of the following best describes the randomisation?**

A) ***No details of randomisation are available, or the method used was inadequate (e.g. randomisation according to the day of the week, even/odd medical record numbers).***

B) An insecure randomisation method was used, where clinical staff could possibly learn of the treatment assignment (e.g. randomisation sequence kept in the clinical area and open/unblinded trial; treatment assignment kept in consecutive ‘sealed’ envelopes and open/unblinded trial).

C) A secure randomisation method was used, where the randomisation sequence was kept away from the clinical area and administered by staff not directly involved in patient care.

The randomisation method used, strictly speaking, followed the definition given in B above because treatment allocation was open. However, in this setting the method used is considered best practice since:

- there are ethical objections to giving placebo infusions, especially in such patients with cancers.
- treatment side effects tend to cause much unblinding anyway (e.g. the rash seen with cetuximab)
- patient out-comes such as survival are not subject to observer bias
- the measures of disease progression were assessed by a group of experts who were independent from the study and who were blind to patient treatment allocations.

There is no likelihood that the main efficacy outcomes for this study were open to bias due to the randomisation methods used.

2.4.2 Adequacy of follow-up

47. **Which of the following best describes the adequacy of follow-up?**

A) ***There were significant numbers of drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates differed between treated and control groups.***

B) There were some drop-outs with no assessment of trial outcome(s) in the subjects who dropped out, and drop-out rates were (approximately) equivalent in treated and control groups.

C) Trial outcome(s) were assessed in all treated and control subjects.

Definition C best described the follow up in this trial. All patients were followed-up for the main efficacy outcomes (whether treatment was followed according to the study protocol or not) and the evaluations made for efficacy included all patients who were randomised on an intention-to-treat basis. Safety evaluations included all patients who received at least one dose of any study therapy. Only a small number of patients in each treatment group failed to comply with study treatment and treatment compliance was balanced between the two study arms.

2.4.3 Blinding of outcomes assessment

48. **Which of the following best describes the blinding of the outcomes assessment?**

A) ***There was an inadequate attempt (or no attempt) to blind observer(s), and the measurement technique was subject to observer bias (e.g. blood pressure measurement with standard sphygmomanometer; measurement of vertebral height on an X-ray).***

B) The observer(s) were kept fully blinded to treatment assignment, or the measurement technique was not subject to observer bias (e.g. measurement of bone mineral density or survival).

Definition B best describes the blinding of outcomes assessment. The predefined efficacy end-points were either not subject to observer bias (survival) or were measured by assessors blinded to treatment assignment (disease response, progression and locoregional control).

49. **Was the design parallel-group or cross-over? Indicate for each cross-over trial whether a carry-over effect is likely.**

This was a two-arm, parallel-group study.

50. **Was the trial conducted in the UK (or were one or more centres of the multinational trial located in the UK)? If not, where was the trial conducted and is clinical practice likely to differ from UK practice?**

The trial was conducted in 15 countries; the USA, 9 EU countries including the UK, Switzerland, Israel, South Africa, Australia and New Zealand. While there is some variation in practice between these countries, practice does not vary sufficiently to prevent the findings of the study being applicable to the UK, all being countries with good standards of health care. Indeed, treatment practices vary between centres in the UK since there are no set treatment guidelines for patients with locally advanced SCCHN[2] and facilities vary from centre to centre[26]. In terms of survival, NICE reports that England and Wales are the same, or slightly better than, the European average[11], indicating that practice is roughly comparable to other European countries.

The study did allow for a range of radiotherapy regimens and this reflects well on the variation in practice in the UK, where all three types of radiotherapy schedule are in use for squamous-cell head and neck cancers. [3]

51. **How do the subjects included in the trial compare with patients who are likely to receive the drug in the UK? Consider factors known to affect outcomes in the main indication such as demographics, epidemiology, disease severity, setting.**

The Bonner study results were obtained in a population whose demographics and characteristics of disease are broadly representative of the target population in the UK i.e. those patients currently receiving radiotherapy alone.

The relevance of the patient population in the Bonner study to the proposed market position in the UK is demonstrated by an audit of 139 patients with locally advanced SCCHN (A+A Healthcare Market Research, Merck KGaA)[3] conducted in the UK between October & November 2005. The audit was conducted because such detailed information was not available in any publicly available databases. 52 physicians from 52 hospitals across the UK provided

information from their last 7 cases treated giving data on 405 patients with SCCHN, 139 of which were locally advanced tumours of the oropharynx, hypopharynx and larynx. The findings showed that patients who are considered appropriate for radiotherapy or chemoradiotherapy treatment are those fit enough to withstand treatment; i.e. the oldest and least fit patients are not given either treatment in the UK.

The median age of UK patients treated with radiotherapy (RT) or chemoradiotherapy (CRT) was 62ys, and 84% of patients had an ECOG performance status between 0 and 1 (= KPS >70). This is similar to those patients treated in the Bonner study. The patient population in the Bonner study therefore is representative of the patient population in the UK who would be considered to receive radiotherapy alone or cetuximab + radiotherapy.

The audit also found that 39% of patients received radiotherapy treatment alone and 41% of patients received concomitant chemoradiotherapy; no particular radiotherapy schedule appeared to be a standard of treatment. This demonstrates that, despite chemoradiotherapy becoming an emerging standard of therapy according to treatment guidelines, there are still 60% of patients in the UK who are of good performance status and relatively young, who do not receive chemoradiotherapy for their locally advanced disease and could be considered for ERT.

Age:

The median age of patients in the Bonner study was 58 (range 35-83) and 56 (range 34-81) years in the RT and ERT treatment arms respectively. This is slightly younger than the mean age of patients in England, which is estimated to be abount 64 years[2] but not disimilar to those patients found to be treated from the A+A Healthcare audit at 62 years. Further, there is some evidence of an increase in these cancers in younger individuals, probably due to changes in smoking and drinking habits.

Gender:

The majority of patients in the Bonner study were male, 79% and 81% in the RT and ERT treatment arms repectively.The proportion of male head & neck cancer patients in England is approx 72% (DAHNO 2006) suggesting that the Bonner study provided a reasonable, if not exact, representation of the English population in terms of gender mix. The A+A Healthcare audit data of patients treated showed that 77% of such patients were male, a very close fit to the Bonner study population.

Risk factors:

Aetiological risk factors for SCCHN cancer are, in particular, tobacco and alcohol[17]. Other risk factors include diet and, possibly, human papillomavirus.[16]

There are marked geographical variations in the incidence of these cancers and in the patterns of individual types of head and neck cancers[14,2]. This is assumed to relate to the variation in exposure to risk factors. Given the nature of the risk factors, it is perhaps not surprising that the incidence of SCCHN tends to be higher in areas of deprivation e.g. carcinoma of the larynx is twice as common in areas of social deprivation[2]. While this leads to variation in the incidence between countries, similar variability is seen within England and Wales between areas of low and high social deprivation.[11]

Overall it can be said that, while the incidence and pattern of SCCHN varies among the countries involved in the study by Bonner, this is not likely to have a marked impact upon the applicability of the study population to the UK patient population, since incidence relates more to variation in risk factors than specific differences in the patient types from one country to another.

General Health:

The inclusion criteria in this study did exclude patients with prior cancers, those with certain marked laboratory abnormalities and those with a low performance status (KPS<60). Further, only a third of patients recruited had a KPS between 60-80%, with two thirds scoring between 90-100%. While this

may be at some variance with the overall population of patients with SCCHN, it is in keeping with the A+A Healthcare audit data in patients receiving treatment with either or both radiotherapy and chemotherapy, 84% of who had an ECOG performance status between 0 and 1 (= KPS >70). It is important to note that some high performance status patients will be excluded from chemoradiotherapy because of specific contraindications to the chemotherapeutic agents. Further, very poor performance status patients are unlikely to be targets for ERT as curative radiotherapy, even on its own, carries substantial toxicity.

Given the principle risk factors of alcohol and tobacco, cardiovascular and respiratory co-morbidity rates tend to be high compared with the general population. There were no exclusion criteria based upon such co-morbidity. Patients with marked abnormalities of liver enzymes were excluded from the study population. This would tend to exclude a proportion of patients from treatment with the cetuximab+radiotherapy combination who have significant alcohol-induced liver-disease.

Furthermore, some patients for whom chemoradiotherapy is not appropriate may be <65y with a PS >80 (i.e. similar to the patient population in the Bonner trial) but with other comorbidities such as impaired renal function or impaired hearing (which preclude the use of cisplatin), or impaired cardiovascular function (which precludes the use of chemoradiotherapy). Such patients would be suitable for cetuximab+ radiotherapy treatment.

52. **For pharmaceuticals, what dosage regimens were used in the trial? Are they within those detailed in the Summary of Product Characteristics?**

The dose of cetuximab in the trial was an initial infusion of 400mg/m^2 at week 1 followed by weekly infusions of 250mg/m^2 for 7 weeks with concurrent radiotherapy during weeks 2 onwards. (6 week schedules of radiotherapy would complete at week 7 and only 7 doses of cetuximab were given).

The dose regimen for cetuximab in the trial is exactly as appears in the SPC. Further, the timing of cetuximab treatment in relation to radiotherapy in the trial is exactly as appears in the SPC.

53. **What was the median (and range) duration of follow-up in the trial?**

The protocol stipulated that patients would be followed up for a minimum of 12 months and for up to five years. Median follow-up times were 54 months in the both groups.

2.5 Results of the comparative randomised trials

54. **Provide the results for all relevant outcome measure(s). If there is more than one trial, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible.**

For each outcome:

- ***describe the unit of measurement***
- ***report the size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic***
- ***provide a 95% confidence interval***
- ***provide the number of patients included in the analysis***
- ***state whether 'intention-to-treat' was used for the analysis***
- ***discuss and justify definitions of any clinically important differences.***

Bonner Study Results

The data given below is from the intention to treat population unless otherwise stated.

Balance between treatment groups

Table 4, gives the base line characteristics of the two treatment groups and shows that these were well balanced for gender, age, race and KPS. Stratification of randomisation by KPS, regional nodes, tumour stage and radiotherapy schedule led to a balanced distribution of these factors between the two treatment groups.

EGFR expression was tested in 81% of patients in the radiotherapy group and 79% of the combination therapy group. EGFR expression was undetectable in only 1% of patients in the radiotherapy group and none of the patients in the combination treatment group. EGFR over-expression is associated with a poor prognosis[6, 7] and with an increased resistance of tumour cells to radiation[8].

The primary tumour site was the oropharynx in 63% and 56% of patients in the RT and ERT groups respectively, the hypopharynx in 13% and 17% respectively and the larynx in 24% and 27% respectively.

Overall, the patients were well balanced between the two treatment groups.

Table 4. Base-line Patient Characteristics, ITT population.*

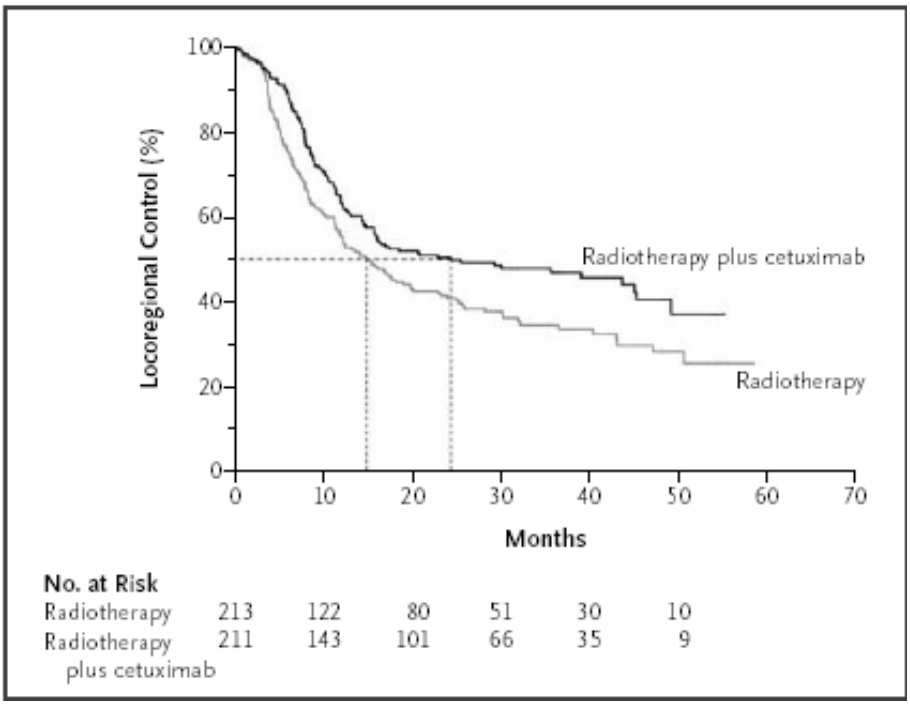
Characteristic	Radiotherapy Alone (N = 213)	Radiotherapy plus Cetuximab (N = 211)	P Value
Age — yr			0.24†
Median	58	56	
Range	35–83	34–81	
Sex — no. (%)			0.72
Male	169 (79)	171 (81)	
Female	44 (21)	40 (19)	
Karnofsky performance score — no. (%)‡			0.47§
60	6 (3)	6 (3)	
70	16 (8)	15 (7)	
80	49 (23)	42 (20)	
90	103 (49)	113 (54)	
100	38 (18)	34 (16)	
Site of primary tumor — no. (%)			0.25
Oropharynx	135 (63)	118 (56)	
Larynx	51 (24)	57 (27)	
Hypopharynx	27 (13)	36 (17)	
American Joint Committee on Cancer stage — no. (%)			0.74
III	52 (24)	55 (26)	
IV	161 (76)	156 (74)	
Tumor stage			0.83
T1	17 (8)	13 (6)	
T2	50 (23)	50 (24)	
T3	81 (38)	85 (40)	
T4	65 (31)	62 (29)	
TX	0	1 (<1)	
Node stage			0.62
N0	38 (18)	42 (20)	
N1	39 (18)	42 (20)	
N2a	21 (10)	12 (6)	
N2b	47 (22)	48 (23)	
N2c	44 (21)	52 (25)	
N3	24 (11)	15 (7)	
EGFR immunostaining — no. (%)			0.66¶
≤50% of cells positive	89 (42)	91 (43)	
>50% of cells positive	81 (38)	75 (36)	
Unknown	40 (19)	45 (21)	
Undetectable	3 (1)	0	

* Percentages may not total 100 because of rounding. P values were determined with the use of Fisher's exact test.
† The P value is for the comparison between patients less than 60 years of age and those 60 years of age or older.
‡ The score was unknown for one patient in each group.
§ The P value is for the comparison between scores of 60, 70, or 80 and scores of 90 or 100.
¶ The P value is for the comparison between positivity of 50 percent or less and positivity of more than 50 percent.

Efficacy Results

The primary end point was locoregional control. The addition of cetuximab to radiotherapy prolonged the duration of locoregional control by almost 10 months compared to radiotherapy alone, with a median duration of 24.4 months versus 14.9 months. (p=0.005, 95% CI 0.52-0.89, hazard ratio 0.68).

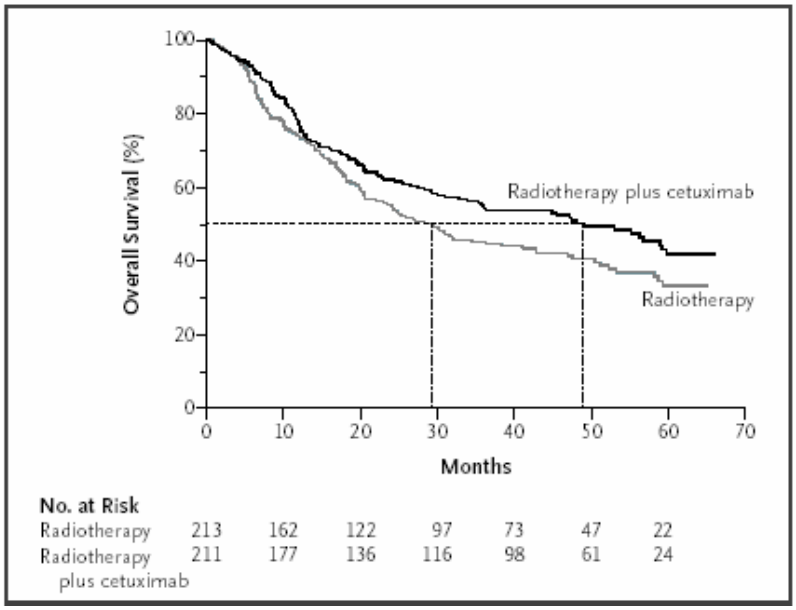
Figure 1. Kaplan-Meier Estimates of Locoregional control (Bonner 2006)



Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.
The hazard ratio for locoregional progression or death in the radiotherapy plus- cetuximab group as compared with the radiotherapy-only group was 0.68 (95 percent confidence interval, 0.52 to 0.89; P = 0.005 by the logrank test). The dotted lines indicate the median durations of locoregional control.

The most important secondary endpoint was survival. The addition of cetuximab to radiotherapy prolonged median overall survival by almost 20 months compared to radiotherapy alone, with a median survival of 49 months versus 29.3 months (p=0.03, HR 0.74, 95% CI: 0.57-0.97).

Figure 2. Kaplan-Meier Estimates of Survival (Bonner 2006)



Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone. The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P = 0.03 by the log-rank test). The dotted lines indicate the median survival times.

A summary table of the efficacy end points is given in Table 5 below.

Table 5. Efficacy Outcomes, Intention to Treat Population.

Variable	Radiotherapy Alone. ITT population N=213	Radiotherapy plus Cetuximab ITT population N=211	P Value	Hazard Ratio	95% CI
Locoregional control Median duration in months	14.9	24.4	0.005	0.68	0.52 -0.89
Progression Free Survival Median duration in months	12.4	17.1	0.006	0.70	0.54 -0.90
Overall Survival Median duration in months	29.3	49.0	0.03	0.74	0.57-0.97
Response Rate (CR+PR) Total number (%)	137 (64%)	155 (74%)	0.02	0.57 (odds ratio)	0.36-0.90

Analyses of sub-groups by tumour site, tumour stage (III or IV) and radiotherapy regimen all showed a trend in favour of the combination therapy for both overall survival and locoregional control, although the study was not powered to detect differences in these subgroups.

Commenting in an editorial accompanying the publication of the pivotal clinical trial, it was noted by Posner and Wirth[27] that sub-group analyses indicated that ERT did not improve survival among patients with hypopharyngeal or laryngeal cancer or when added to non-hyperfractionated radiotherapy.

Please note that it is misleading to draw conclusions from the analysis of sub-groups of patients, especially a lack of significance, as the Bonner study was not powered to show meaningful differences in sub-group analyses and any failure to demonstrate a statistically significant outcome is generally due to a lack of numbers within the sub groups analysed, rather than an indication that the overall study results are not applicable to that sub group.

With this caveat, for completeness, the results for the main subgroup analyses for the intention to treat population as presented in Bonner et al 2006 /EMR 62 202-006 are given in Table 6.

Table 6. Sub Group Analyses; Intention to Treat Population.

	Radiotherapy Alone (N = 213)	Radiotherapy plus Cetuximab (N = 211)	Hazard Ratio
Overall Survival. Median duration in months according to radiotherapy regimen.			
Once daily	15.3 (n=55)	18.9 (n=50)	1.01
Twice daily	53.3 (n=37)	58.9 (n=38)	0.74
Concomitant boost	31.0 (n=120)	>66.0 (n=117)	0.64
Locoregional Control. Median duration in months according to radiotherapy regimen			
Once daily	8.5 (n=55)	11.9 (n=50)	0.73
Twice daily	19.9 (n=37)	54.1+ (n=38)	0.82
Concomitant boost	17.7 (n=120)	45.1+ (n=117)	0.62
Overall Survival. Median duration in months according to tumour Site.			
Oropharynx	30.3 (n=135)	>66.0 (n=118)	0.62
Larynx	31.6 (n=51)	32.8 (n=57)	0.87
hypopharynx	13.5 (n=27)	13.7 (n=36)	0.94
Locoregional Control. Median duration in months according to tumour site			
Oropharynx	23.0 (n=135)	49.0 (n=118)	0.61
Larynx	11.9 (n=51)	12.9 (n=57)	0.69
hypopharynx	10.3 (n=27)	12.5 (n=36)	0.92
Overall Survival. Median duration in months according to tumour stage.			
AJCC III	42.9 (n=52)	55.2 (n=55)	0.77
AJCC IV	24.2 (n=161)	47.4 (n=156)	0.77
Locoregional control. Median duration in months according to tumour stage.			
AJCC III	16.2 (n=52)	38.9 (n=55)	0.69
AJCC IV	13.5 (n=161)	20.9 (n=156)	0.73

+ denotes that the median had not been reached at cut-off

Quality of Life

A total of 424 patients were enrolled in the study. Two patients did not complete either QoL questionnaire; three patients completed a questionnaire but they were considered non-evaluable. Thus 419 patients were included in the QoL analysis (212 in the RT arm and 207 in the ERT arm).

The general pattern for the QoL scales is an initial decrease at post baseline visits compared to baseline in the mean scores; by month 12 the scores increase and are comparable to the baseline. QoL improved in the ERT arm for swallowing (p=0.004) and speech problems (p=0.028) at week four on both scales. The differences were small and the results were not supported at other time-points or by summary measure analysis.

There is a small difference (non-significant) in mean scores at baseline between the two treatments groups - this difference remains throughout the study. At all time points the 95% confidence interval for the difference in treatment groups includes 0 indicating that the treatment difference is not statistically significant.

Overall, this analysis suggests that the addition of Erbitux does not have a negative effect on global health status\QoL scores including social functioning, social eating and social contact.

55. **Where interim trial data are quoted this should be clearly stated along with the point at which data were taken and the time remaining until completion of that trial. Analytical adjustments should be described to cater for the interim nature of the data.**

Not applicable

56. **If the trial measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.**

Not applicable

57. **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**

Not applicable

2.6 Meta-analysis

58. **Where more than one study is available consideration should be given to undertaking a meta-analysis. The following steps should be used as a minimum.**

- ***Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate the trial results are heterogeneous, try to provide an explanation for the heterogeneity.***
- ***Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).***
- ***Provide an adequate description of the methods of statistical combination and justify their choice.***
- ***Undertake sensitivity analysis where appropriate***
- ***Tabulate and/or graphically display the individual and combined results.***

Not relevant as only one applicable randomised controlled trial.

2.7 Indirect/mixed treatment comparisons

59. **In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest consideration should be given to using indirect/mixed treatment comparisons. Give a full description of the methodology used and provide a justification for the approach.**

Not applicable as direct comparison available for the intended target population for this treatment intervention i.e. those patients currently receiving radiotherapy alone.

2.8 Comparative safety

60. **Give a brief overview of the safety of the technology compared to the comparator(s). Give incidence rates if appropriate.**

Evidence from comparative trials and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate a relative lack of adverse effects commonly associated with the comparator or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are primarily designed to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to incidence of an adverse effect) these should be reported here in the same detail as described previously (section 3) for efficacy trials.

The Bonner Study demonstrated that this treatment combination had a very acceptable safety profile.

Erbitux did not significantly exacerbate the toxicities associated with radiotherapy, such as xerostomia, dysphagia and, in particular, mucositis. This is important because these side effects lead to the need for gastric feeding tubes, sometimes permanently, or the need for repeated oesophageal dilation in the months following treatment [16,28] . This contrasts with chemoradiotherapy where the toxicities can be treatment-limiting and where severe mucositis can be a particular problem.[5]

The most common side-effect seen with cetuximab was an acne-like rash. The majority of skin reactions develop within the first three weeks of therapy and generally resolve without sequelae following appropriate intervention by dose delay or completion of treatment[29]. The excess of pruritis seen in the combination treatment arm is thought to relate to the skin rash.

The other, less common but important side effect seen with cetuximab were hypersensitivity (infusion) reactions. Such reactions may lead to dose reductions or the cessation of treatment.

Both of these side effects are consistent with the SPC for Erbitux. Headaches, chills and fever, which were all seen in excess in the combination treatment arm, are all known effects of monoclonal antibodies.

A summary of the safety data from the Bonner study can be found in Table 7. The analysis was performed on the “as-treated population” i.e all subjects who received at least one dose of cetuximab or one fraction of radiotherapy.

Table 7. Adverse Events.*

Adverse Event	Radiotherapy Alone (N = 212)		Radiotherapy plus Cetuximab (N = 208)		P Value †	
	All Grades	Grades 3–5	All Grades	Grades 3–5	All Grades	Grades 3–5
	percent of patients					
Mucositis	94	52	93	56	0.84	0.44
Acneiform rash	10	1	87	17	<0.001	<0.001
Radiation dermatitis	90	18	86	23	0.24	0.27
Weight loss	72	7	84	11	0.005	0.12
Xerostomia	71	3	72	5	0.83	0.32
Dysphagia	63	30	65	26	0.68	0.45
Asthenia	49	5	56	4	0.17	0.64
Nausea	37	2	49	2	0.02	1.00
Constipation	30	5	35	5	0.35	1.00
Taste perversion	28	0	29	0	0.83	—
Vomiting	23	4	29	2	0.18	0.42
Pain	28	7	28	6	1.00	0.84
Anorexia	23	2	27	2	0.26	1.00
Fever	13	1	26	1	0.001	1.00
Pharyngitis	19	4	26	3	0.10	0.80
Dehydration	19	8	25	6	0.16	0.57
Oral candidiasis	22	0	20	0	0.63	—
Coughing	19	0	20	<1	1.00	0.50
Voice alteration	22	0	19	2	0.47	0.06
Diarrhea	13	1	19	2	0.11	0.50
Headache	8	<1	19	<1	0.001	1.00
Pruritus	4	0	16	0	<0.001	—
Infusion reaction	2	0	15	3	<0.001	0.01
Insomnia	14	0	15	0	0.89	—
Dyspepsia	9	1	14	0	0.13	0.50
Increased sputum	15	1	13	<1	0.78	0.62
Infection	9	1	13	1	0.28	1.00
Anxiety	9	1	11	<1	0.75	1.00
Chills	5	0	11	0	0.03	—
Anemia	13	6	3	1	<0.001	0.006

* Adverse events that occurred in at least 10 percent of patients in either treatment group are shown, regardless of cause.
† P values were determined with the use of the Fisher exact test

2.9 Interpretation of clinical evidence

61. **Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.**

The addition of cetuximab to radiotherapy resulted in clinically meaningful benefits:

- Improved median duration of locoregional control by 9.5 months.
- Prolonged median overall survival by 19.7 months with a 26% reduction in the risk of death.
- Significantly improved progression-free survival, with a median of 17.1 months compared to 12.4 months in those patients treated with radiotherapy alone.
- When used in combination with radiotherapy, cetuximab does not significantly exacerbate the toxicities associated with radiotherapy.

Indeed, the survival advantage of nearly 20 months is greater than the survival advantages of 7–18 months seen in large, randomised studies of chemoradiotherapy versus radiotherapy[30, 31, 32, 33].

For a substantial number of patients who are currently treated with radiotherapy alone, the combination of cetuximab plus radiotherapy provides an important treatment option. While some of these patients may have different profiles from those included in the Bonner study, many will fit the criteria used in this study. Of these, most should be able to benefit from this combination treatment since contraindications to cetuximab are limited.

62. **Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, issues relating to conduct of the trial versus clinical practice or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?**

Suitable patients for the combination of radiotherapy and cetuximab would be those who have locally advanced SCCHN (squamous cell carcinomas of the oropharynx, larynx and hypopharynx) who are considered suitable for radiotherapy but not for chemoradiotherapy (currently about 39% of UK patients) and who have no contraindication to cetuximab therapy[3]. While many of the fittest patients are likely to receive treatment with radiotherapy and chemotherapy, those currently receiving curative regimens of radiotherapy as monotherapy are unlikely to have Karnofsky Performance Status much below that of the patients included in the Bonner trial i.e. 60-100. (A KPS of 40 or less corresponds to patients unable to care for themselves and in institutional or hospital care and a KPS score of 50 corresponds to a patient requiring considerable assistance and frequent medical care).

The dose regimen recommended in the SPC corresponds exactly with that in the Bonner study and, therefore, 100% of the evidence base.

In clinical terms, the combination of cetuximab plus radiotherapy is a highly effective and well tolerated treatment regime that would benefit patients similar to those included in the Bonner study who are considered unsuitable for chemoradiotherapy. Treatment should be given according to the doses and schedules included in this study.

3 Cost effectiveness

3.1 Published cost-effectiveness estimates

3.1.1 Identification and description of studies

63. **Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the company. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced and the rationale for any inclusion and exclusion criteria used should be provided.**

A search strategy was developed to identify key papers which could provide cost-effectiveness data for the assessment of Cetuximab therapy in squamous cell carcinoma of the head and neck (SCCHN).

64. **the specific databases searched and service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:**

- ***Medline***
- ***Embase***
- ***Medline (R) In-Process***
- ***Health Economic Evaluation Database***
- ***NHS Economic Evaluation Database (NHS EED)***

Searches were performed in OVID for the following databases:

- Medline
- Embase

Searches were also performed in the Cochrane Library for the following databases:

- The Cochrane Database of Systematic Reviews (Cochrane Reviews)
- DARE, Database of Abstracts of Reviews of Effects (Other Reviews)
- The Cochrane Central Register of Controlled Trials (Clinical Trials)

- HTA, Health Technology Assessment Database (Technology Assessments)
- NHS EED, NHS Economic Evaluation Database (Economic Evaluations)

65. **The date the search was conducted**

The search was conducted on June 28th-29th 2006.

66. **The date span of the search**

The date spans for the searches varied by database. The Cochrane library databases were all searched from the year 1800 to 2006. The OVID databases were searched from:

- Medline - 1996 to (June week 3) 2006
- Embase - 1980 to (week 25) 2006

67. **The complete search strategies used, including all the search terms: Textwords (free text), Subject Index Headings (e.g. MeSH) and the relationship between the search terms (e.g. Boolean)**

The systematic review sought to identify all studies evaluating the cost-effectiveness of cetuximab for head and neck squamous cell carcinoma.

Key search terms were identified and combined in the search strategy to identify relevant papers, see list below:

- Head and neck cancer
- Squamous cell carcinoma
- Erbitux or cetuximab
- costs and cost analysis
- economics
- economic models
- value of life

- quality adjusted life years
- utilization review
- delivery of health care/utility
- cost (effectiveness or utility or benefit)
- cost (minimum or study or efficacy)
- economic evaluation or analysis
- resource utility
- economic or pharmacoeconomic
- health economics
- journal of health economics
- research in health economics
- pharmacoeconomics
- value in health
- health care utilization
- hospital bed utilization
- hospital utilization
- "HEPAC health economics in prevention and care”

Table 8 Search strategy used for Medline –1996 to (June week 3) 2006

	Search history	References retrieved
1	Exp head and neck cancer/	1418
2	(((squamous cell carcinoma$ or squamous-cell carcinoma$) adj head and neck$) or HNSCC).ti,ab.	1227
3	Erbitux or Cetuximab. ti,ab.	398
4	or/1-3	3036
5	4 and exp "costs and cost analysis"/	7
6	4 and economics/	7
7	4 and exp models, economic/	0
8	4 and value of life/	1
9	4 and quality-adjusted life years	1
10	4 and ec.fs.	1
11	4 and exp utilization review/	11
12	4 and delivery of health care/ut	0
13	4 and (cost$ adj5 (effect$ or utili$ or benefit$)).ti,ab.	0
14	4 and (cost$ adj5 (minim$ or stud$ or effic$)).ti,ab.	9
15	4 and (economic$ adj5 (evaluat$ or analy$)).ti,ab.	2
16	4 and (resource$ adj5 utili$).ti,ab.	2
17	4 and (economic$ or pharmacoeconomic$).ti,ab.	1
18	4 and health economics.jn.	6
19	4 and journal of health economics.jn.	0
20	4 and research in health economics.jn.	0
21	4 and pharmacoeconomics.jn.	0
22	4 and value in health.jn.	0
23	or/5-22	23

Table 9 Search strategy used for Embase – 1980 to (week 25) 2006

	Search history	References retrieved
1	Exp head and neck cancer/	34
2	(((squamous cell carcinoma$ or squamous-cell carcinoma$) adj head and neck$) or HNSSC).ti,ab.	2507
3	Erbitux or Cetuximab.ti,ab.	884
4	or/1-3	3414
5	4 and health economics/	3
6	4 and exp economic evaluation/	41
7	4 and exp pharmacoeconomics/	142
8	4 and pe.fs.	81
9	4 and quality adjusted life year	2
10	4 and exp head and neck cancer/dm	0
11	4 and economics/	0
12	4 and finance/	0
13	4 and health care utilization/	2
14	4 and hospital bed utilization/	0
15	4 and hospital utilization/	0
16	4 and (cost$ adj5 (effect$ or utili$ or benefit$)).ti,ab.	13
17	4 and (cost$ adj5 (minim$ or stud$ or effic$)).ti,ab.	10
18	4 and (economic$ adj5 (evaluat$ or analy$)).ti,ab.	2
19	4 and (resource$ adj5 utili$).ti,ab.	2
20	4 and (economic$ or pharmacoeconomic$).ti,ab.	14
21	4 and health economics.jn.	0
22	4 and "HEPAC health economics in prevention and care".jn.	0
23	4 and health economics.jn.	0
24	4 and journal of health economics.jn.	0
25	4 and pharmacoeconomics.jn.	0
26	4 and value in health.jn.	1
27	or/5-26	204
28	Limit English language and humans	174

Search strategy used for Cochrane Library (including NHSEED and DARE)

	Search history	References retrieved
1	Exp head and neck cancer	33
2	(((squamous cell carcinoma$ or squamous-cell carcinoma$) adj head and neck$) or HNSSC).ti,ab.	15
3	(Erbitux or Cetuximab)	0
4	#1 or #2 or #3	0

68. **Details of any additional searches, for example searches of company databases. Include a description of each database**

Published NICE guidelines and technology appraisals were scanned for relevant studies. An internal consultation with medical colleagues and external key opinion leaders was carried out to identify further research.

69. **The inclusion and exclusion criteria**

Date of publication: The date restrictions were broadly from 1980 to 2006.

Language of publication: Only studies published in English were included in systematic review.

Type of study and outcome measures: Studies were included within the systematic review if they described an economic evaluation. However, no restrictions were placed on the type of economic evaluation or outcomes reported.

Intervention: Studies were only included if they evaluated cetuximab in head and neck cancer. However, no restrictions were imposed on the presence or nature of interventions used in combination with cetuximab or the comparator used in the studies.

Subjects: Studies were only included in the systematic review, if they concerned humans with a diagnosis of head and neck cancer (specifically head and neck squamous cell carcinoma). No restrictions were placed on the age or gender of patients included in the analysis.

70. **The data abstraction strategy.**

Not applicable.

3.1.2 Description of identified studies

71. **Please provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales.**

No studies were identified which met the inclusion criteria of the search, see Table 10 and 11 below.

Table 10 Results of literature search for economic evaluations on head and neck cancer

Databases (dates covered)	Number of articles found	After excluding duplicates
Medline (1996 to June week 3 2006)	23	22
EMBASE (1980 to week 25 2006)	174	168
Cochrane Library (including NHSEED, DARE and HTA) (1880 to May 2006)	0	0
Manual searching	0	0
Total	197	190

Abbreviations: NHS EED, National Health Services Economic Evaluation database; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment

Table 11 Number of papers excluded and reasons for exclusion

Reason for exclusion	Number of studies excluded
Evaluation was not directly related head and neck cancer	160
Failed to include an economic evaluation or health economics did not form part of the review/study	26
Did not involve the evaluation of Erbitux/ Cetuximab	4
Total number of publications excluded	190
Total number of publications for review	0

3.2 De novo economic evaluation(s)

72. **In the absence of a relevant published economic evaluation, manufacturers should submit their own economic evaluation.**

A de novo economic evaluation is presented in this submission. The economic evaluation compares the costs and health outcomes of patients with locally advanced head & neck cancer of two treatment strategies, cetuximab in combination with radiotherapy (ERT) and radiotherapy alone (RT).

The economic evaluation is delineated into two distinct phases. In the first phase, costs and outcomes are estimated based on the reported dataset from the pivotal clinical trial (Bonner et al., 2006/EMR 62 202-006). Estimates are based on actual observations from the Bonner trial. In the second phase,

where trial observations are censored, patient survival is extrapolated via a statistical parametric model and imputed costs and health outcomes estimated thereon.

Combining the two phases allows the estimation of patient-level costs of treatment and health outcomes for each individual. The average of these individual estimates in each treatment group provides the basis for the incremental analysis. With health outcomes estimated in quality-adjusted life years (QALYs), the economic evaluation takes the form of a cost-utility analysis (CUA).

3.2.1 A note on the Reference Case

73. **When estimating cost effectiveness, particular emphasis should be given to adhering to the 'Reference Case' (see NICE 'Guide to the Methods of Technology Appraisal'). Reasons for deviating from it should be clearly explained. Particularly important features of the reference case include:**

Attribute	Reference case	Section in Methods Guide
Comparator(s)	Alternative therapies including those routinely used in NHS	5.3.2
Perspective costs	NHS and PSS	5.3.3
Perspective benefits	All health effects on individuals	5.3.3
Form of EE	CEA	5.3.4
Time horizon	Sufficient to capture differences in costs and outcomes	5.3.5
Synthesis of evidence	Systematic review	5.4.1
Outcome measure	QALYs	5.5
Health states for QALY measurement	Described using a standardised and validated instrument	5.5
Benefit valuation	Time Trade Off or Standard Gamble	5.5
Source of preference data	Sample of public	5.5
Discount rate	Health benefits and costs 3.5%	5.7.2
Equity	No special weighting	5.9.7
Sensitivity analysis	Probabilistic sensitivity analysis	5.9.3

3.2.2 Technology

74. **How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.**

The purpose of this *de novo* economic evaluation is to estimate the cost-effectiveness of cetuximab in combination with radiotherapy (ERT) compared to radiotherapy alone (RT), in the treatment of locally advanced head and neck cancer in those patients who are considered inappropriate for chemoradiotherapy but suitable for radiotherapy.

Although the economic evaluation is trial-based, there is also a modelling component with regards to the extrapolation of health effects beyond the trial period.

It is assumed that the treatment regimens are as set out in the trial protocol and administered as recorded in the trial dataset (Bonner *et al.*, 2006/EMR 62 202-006). Cetuximab was administered as follows:

- Initial loading dose of 400 mg/m^2 1 week prior to the start of radiotherapy
- Subsequent doses of 250 mg/m^2 once per week for duration of radiotherapy

Both treatment groups received radiotherapy based on one of the regimens specified in **Table 12**.

Table 12 Radiotherapy regimens

Regimen	Total radiation dose	Once-daily fractions	Twice-daily fractions
Once-daily	70.0 Gy in 35 fractions	2.0 Gy/fraction; 5 fractions/week for 7 weeks	Not applicable
Twice-daily	72.0-76.8 Gy in 60-64 fractions	Not applicable	1.2 Gy/fraction; 10 fractions/week for 6.0-6.5 weeks
Concomitant boost	72.0 Gy in 42 fractions	32.4 Gy; 1.8 Gy/fraction; 5 fractions/week for 3.6 weeks	Morning dose: 21.6 Gy; 1.8 Gy/fraction; 5 fractions/week for 2.4 weeks Afternoon dose: 18.0 Gy; 1.5 Gy/fraction; 5 fractions/week for 2.4 weeks

Source: Bonner *et al*. (2006)

Treatment lasted for a maximum of 8 weeks and the purpose of the *de novo* economic evaluation is to assess the long-term comparative impact of treatment.

3.2.3 Evaluation design and structure

3.2.3.1 Patients

75. **What group(s) of patients is / are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the decision problem; in other words, specify the data-gap.**

The population of the pivotal clinical trial (Bonner *et al.*, 2006/EMR 62 202-006) is considered in the economic evaluation, that is, those with locally advanced head and neck cancer. This is in line with the licensed indication for ERT. The proposed use in England & Wales is restricted to locally advanced head and neck cancer patients who are considered inappropriate for chemoradiotherapy but suitable for radiotherapy.

The economic evaluation population is potentially different to the proposed market position in that it is based on the pivotal trial population and the trial did not explicitly recruit patients who were considered inappropriate for

chemoradiotherapy but suitable for radiotherapy. However, the relevance of the patient population in the Bonner study to the proposed market position in the UK can be proven using an audit of 139 patients with locally advanced SCCHN (A+A Healthcare Market Research, Merck KGaA) conducted in the UK between October & November 2005. This audit was conducted to provide detailed information on the relevant patient population as this was not available in any publicly available database.

In the A+A Healthcare Market Research audit the median age of patients treated with radiotherapy (RT) or chemoradiotherapy (CRT) was 62 years. The median age in Bonner et al was 58 (range 35-83) and 56 (range 34-81) years in the two treatment arms. The A+A Healthcare market research found that 77% of patients treated were male. The majority of patients in the Bonner study were male, 79% and 81% in the two treatment arms repectively. 84% of patients in the A+A Healthcare market research audit had an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 1 (= KPS >70). This is similar to patients treated in the Bonner study.

The A+A healthcare market research audit also found:

- 39% of patients received radiotherapy treatment alone
- 41% of patients received concomitant chemoradiotherapy
- No particular radiotherapy schedule appeared to be standard treatment

Further detail can be found in section 2.4.3 (question 51).

It is also worth consideration that the use of chemoradiotherapy may be inappropriate in some patients due to comorbidities such as impaired renal function or impaired hearing (which preclude the use of cisplatin), or impaired cardiovascular function (which precludes the use of chemoradiotherapy).

76. **Was the analysis carried out for any subgroups of patients? If so, how was this subgroup identified, what clinical information is there to support the biological plausibility and how was the statistical analysis undertaken?**

No subgroup data analysis was performed because the full trial population was appropriate for the economic evaluation.

We do not believe it would be appropriate to conduct economic modelling on the sub-group analyses conducted on the clinical trial data because the Bonner study was not powered to show meaningful differences in sub-group analyses.

77. **Were any obvious subgroups not considered? If so, which ones, and why were they not considered?**

No obvious sub-groups appropriate for economic modelling were ignored.

Analyses of sub-groups by tumour site, tumour stage (III or IV) and radiotherapy regimen all showed a trend in favour of the combination therapy for both overall survival and locoregional control, although the study was not powered to detect differences in these subgroups. Commenting in an editorial accompanying the publication of the pivotal clinical trial, it was noted by Posner and Wirth that sub-group analyses indicated that ERT did not improve survival among patients with hypopharyngeal or laryngeal cancer or when added to non-hyperfractionated radiotherapy.

However, it is misleading to draw conclusions from the analysis of sub-groups of patients, as the Bonner study was not powered to show meaningful differences in sub-group analyses and any failure to demonstrate a statistically significant outcome is generally due to a lack of numbers within the sub groups analysed, rather than an indication that the overall study results are not applicable to that sub group. This was stated by Bonner in the publication.

78. **At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?**

Patients enter the economic evaluation at the commencement of induction therapy for SCCHN and exit at the point of death.

3.2.4 Comparator technology

79. **What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the information provided in Section X of your submission.**

The comparator therapy in the economic evaluation is radiotherapy alone (RT). This is the comparator arm of the pivotal clinical trial (Bonner *et al*., 2006/EMR 62 202-006) and it is the appropriate comparator for the patient population defined in questions 75 and 76 above.

3.2.5 Study perspective

80. **Did the perspective reflect NICE's Reference Case? If not, how and why did it differ?**

The perspective of the economic evaluation matches that of the NICE Reference Case. Costs are estimated from the perspective of the NHS and all relevant disease and treatment health effects to the individual are captured via quality-adjusted life years (QALYs).

81. **What time horizon was used in the analysis and what was the justification for this choice?**

Given that treatment affects mortality, the economic evaluation has a lifetime time horizon in order to fully capture the long term impact of the comparative survival associated with treatment, in addition to patient quality of life and costs. Where data were censored in the clinical trial (Bonner *et al*., 2006/EMR 62 202-006), patient costs and health effects are extrapolated in the economic model. The impact of other time horizons is assessed in sensitivity analysis.

3.2.6 Framework

3.2.6.1 Model-based evaluations

82. **Please provide the following.**

- ***Description of the model type.***
- ***A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.***
- ***A list of all variables that includes their value, range (distribution) and source.***
- ***A separate list of all assumptions and a justification for each assumption.***

- **Description of the model type:**

The foundation of the economic model is a patient-level analysis of the reported dataset from the pivotal head-to-head clinical trial (Bonner *et al*., 2006/EMR 62 202-006). The model uses the individual patient-level analysis to estimate costs and health effects for each patient during the trial period and then extrapolates where data were censored. The individual patient estimates of costs and health effects over the full time horizon are used to calculate mean values for each treatment group and to estimate distributions via bootstrapping.

The economic model was constructed entirely in MS Excel.

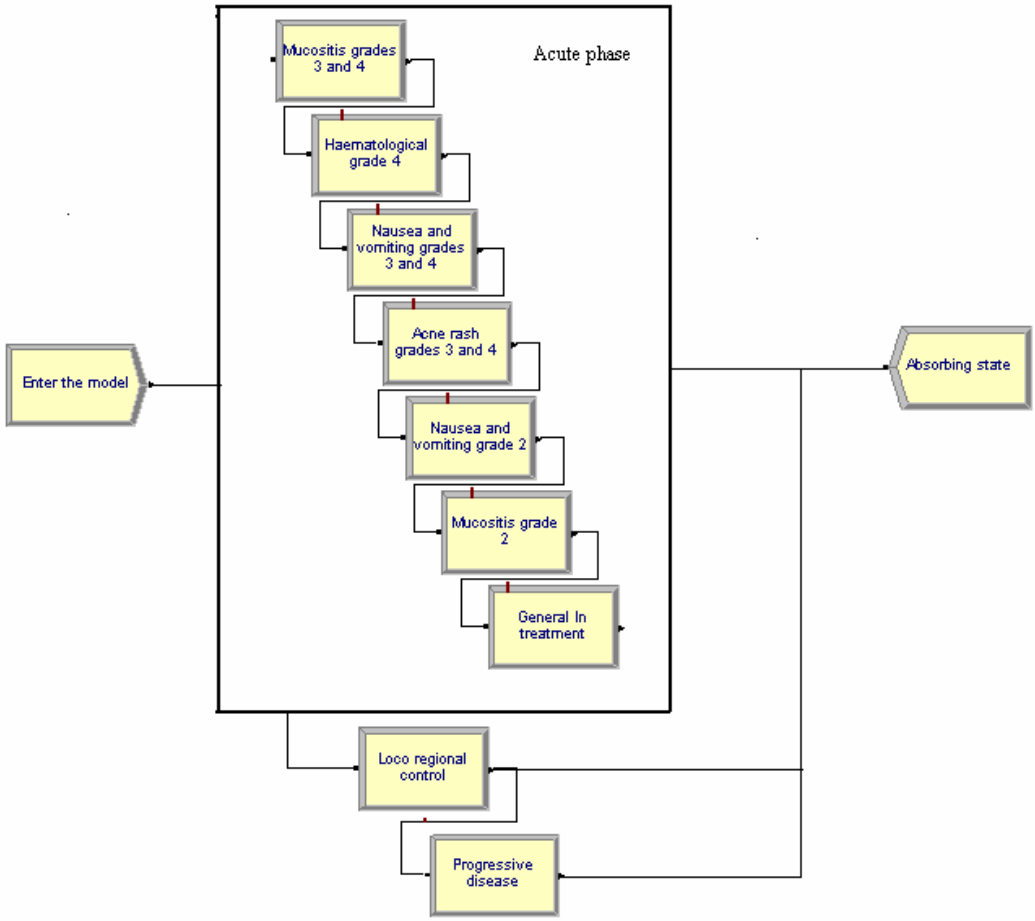
- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

Figure 3 presents an illustration of the model structure. The box surrounding the acute phase health states represents the clear delineation between the valuation of patient quality of life in the acute and post-treatment phases.

Patients enter the model at the beginning of the trial period and enter the acute treatment phase. During the acute phase, patients reside in the health state representing their worst adverse event(s) according to the algorithm outlined later in this section. Following the acute phase, patients enter the locoregional control health state and remain there until they experience disease progression at which point they enter the progressive disease health state. Patients flow in only one direction from acute phase to locoregional control to progressive disease, e.g. it is not possible for patients to go from progressive disease back to locoregional control etc. Finally, at any point in the model patients may exit the model and enter the absorbing state (death).

Costs are accumulated as appropriate throughout the model.

Figure 3 Model Schematic



- **A list of all variables that includes their value, range (distribution) and source.**

Table 13 present the cost variables for each resource category and their values in the base case analysis. It is important to note that the variables presented are the end values used in each case and represent the final values used to calculate the resource utilisation for trial patients, however, other root variables may feed into these values. Where the derivation of the variable is simple, its source is listed. Otherwise, a full description of the derivation of each variable is included in Technical Appendix 1.

Table 13 Cost variables

Variable	Value in base case	Description	Source/derivation
Acute phase adverse event episode costs			
Acne/rash grade 3 episode cost	**£43.38**	Expected cost of hospitalisations, medication and procedures associated with event per patient	See Technical Appendix 1
Acne/rash grade 4 episode cost	**£43.38**	As above	See Technical Appendix 1
Anaemia grade 3 episode cost	**£930.04**	As above	See Technical Appendix 1
Anaemia grade 4 episode cost	**£930.04**	As above	See Technical Appendix 1
Dehydration grade 3 episode cost	**£1,519.05**	As above	See Technical Appendix 1
Dehydration grade 4 episode cost	**£1,519.05**	As above	See Technical Appendix 1
Febrile neutropenia grade 3 episode cost	**£1,337.42**	As above	See Technical Appendix 1
Febrile neutropenia grade 4 episode cost	**£1,337.42**	As above	See Technical Appendix 1
Fever grade 3 episode cost	**£1,103.37**	As above	See Technical Appendix 1
Fever grade 4 episode cost	**£1,103.37**	As above	See Technical Appendix 1
Mucositis/stomatitis/dysphagia grade 2 episode cost	**£94.72**	As above	See Technical Appendix 1
Mucositis/stomatitis/dysphagia grade 3 episode cost	**£307.18**	As above	See Technical Appendix 1
Mucositis/stomatitis/dysphagia grade 4 episode cost	**£3,035.70**	As above	See Technical Appendix 1
Nausea & vomiting grade 2 episode cost	**£80.68**	As above	See Technical Appendix 1
Nausea & vomiting grade 3 episode cost	**£333.29**	As above	See Technical Appendix 1
Nausea & vomiting grade 4 episode cost	**£1,099.06**	As above	See Technical Appendix 1
Radiation dermatitis grade 3 episode cost	**£6.36**	As above	See Technical Appendix 1
Radiation dermatitis grade 4 episode cost	**£6.36**	As above	See Technical Appendix 1
Thrombocytopenia grade 3 episode cost	**£84.22**	As above	See Technical Appendix 1
Thrombocytopenia grade 4 episode cost	**£84.22**	As above	See Technical Appendix 1

Variable	Value in base case	Description	Source/derivation
Imaging costs by time period			
Imaging during staging and first year post-treatment	**£183.16**	Expected cost of imaging scans during staging and 1st year post-treatment per patient	Staging: £124.51 (100% receiving CT scan + 30% receiving MRI scan) Year 1: £58.66
Imaging year 2 post-treatment	**£58.66**	Expected cost of imaging scans during 2nd year post-treatment per patient	One CT scan; NHS Reference Costs - Band C4 - CT Radiotherapy Planning RBC4 Appendix SRC4lii
Imaging year 3 post-treatment	**£134.33**	Expected cost of imaging scans during 3rd year post-treatment per patient	One CT scan + 5% receiving PET scan + 100% receiving X-ray test.
Routine monitoring costs			
Routine monitoring up to 5 weeks post-treatment; weekly visits	£464.99	Expected cost of specialist follow-up visits up to 5 weeks post-treatment per patient	Five weekly visits; Specialty code 800 (Clinical oncology) - Subsequent visit
Routine monitoring up to 1 year post-treatment; monthly visits	£1,116.00	Expected cost of specialist follow-up visits up to 1 year post-treatment per patient	Montlhy visits
Routine monitoring up to 2 years post-treatment; 2-monthly visits	£558.00	Expected cost of specialist follow-up visits up to 2 years post-treatment per patient	2-montlhy visits
Routine monitoring up to 4 years post-treatment; 3-monthly visits	£372.00	Expected cost of specialist follow-up visits up to 4 years post-treatment per patient	3-monthly visits
Procedure costs			
Percutaneous Endoscopic Gastronomy (PEG)	£111.77	Expected cost of PEG insertion per patient	10% receiveing PEG; HRG F04 - Therapeutic endoscopic procedures (ELIP)
Palliative care			
One-off cost at progression (RT Group)	£1,251.54	Expected cost of secondary treatment per patient	See Technical Appendix 1
One-off cost at progression (ERT Group)	£1,252.31	As above	See Technical Appendix 1

Variable	Value in base case	Description	Source/derivation
Study drug			
Cetuximab	£136.50	Unit cost per vial	100mg; Erbitux 2mg/ml; MIMS March 2005
Radiotherapy treatment			
Once daily, course >23 fractions	£2,666.99	Expected cost of radiotherapy treatment per patient receiving once-daily radiotherapy and a crse of more than 23 fractions	Weighted average; HRG w24 Teletherapy with Technical Support and Multiple Planning, >23 Fractions + HRG w23 Teletherapy with Technical Support, >23 FractionsHRG w24 Teletherapy with Technical Support and Multiple Planning, >23 Fractions
Twice daily or concomitant boost	£2,675.57	Expected cost of radiotherapy treatment per patient receiving twice-daily or concomitant boost radiotherapy	Weighted average; HRG w26 Teletherapy with Technical Support and Multiple Planning, Hyperfractionation + HRG w25 Teletherapy with Technical Support, HyperfractionationHRG w26 Teletherapy with Technical Support and Multiple Planning, Hyperfractionation
Once daily, course <4 fractions	£919.16	Expected cost of radiotherapy treatment per patient receiving once-daily radiotherapy and a crse of less than 4 fractions	Weighted average; HRG w20 Teletherapy with Technical Support, <4 Fractions
Once daily, course >3 and <13 fractions	£1,135.93	Expected cost of radiotherapy treatment per patient receiving once-daily radiotherapy and a crse of between 4 and 12 fractions	Weighted average; HRG w21 Teletherapy with Technical Support, >3 <13 Fractions
Once daily, course >12 and <24 fractions	£1,879.77	Expected cost of radiotherapy treatment per patient receiving once-daily radiotherapy and a crse of between 13 and 23 fractions	Weighted average; HRG w22 Teletherapy with Technical Support, >12 <24 Fractions
Administration			
Radiotherapy administration: Outpatient initial visit	£141.61	Unit cost of specialist visit	Specialty code RADY (No treatment) - Initial visit
Radiotherapy administration: Outpatient subsequent visit	£88.31	As above	Specialty code RADY (No treatment) - Subsequent visit
Cetuximab administration: Outpatient initial visit	£178.66	As above	Specialty code 370 (Medical Oncology) - Initial visit
Cetuximab administration: Outpatient subsequent visit	£124.66	As above	Specialty code 370 (Medical Oncology) - Subsequent visit

Table 14 presents the health state utilities used in the economic model.

Table 14 Health state utilities

Health State	Utility	Source
Acute phase health states		
A - General In-Treatment	0.659	See Technical Appendix 1
B – Mucositis/Dysphagia/Stomatitis Grade 3 or 4	0.062	See Technical Appendix 1
C - Mucositis/Dysphagia/Stomatitis Grade 2	0.608	See Technical Appendix 1
D – Nausea & Vomiting Grade 3 or 4	0.108	See Technical Appendix 1
E - Nausea & Vomiting Grade 2	0.573	See Technical Appendix 1
F – Acne/Rash Grade 3 or 4	0.226	See Technical Appendix 1
G - Haemotological Grade 4	0.101	See Technical Appendix 1
Post-treatment health states		
J - Locoregional control	0.862	See Technical Appendix 1
K - Progressive disease	0.129	See Technical Appendix 1

- **A separate list of all assumptions and a justification for each assumption.**

Table 15 presents a list of all assumptions for costs by category of resource use and health outcomes. Where assumptions were necessary, expert opinion was sought as validation. A panel of 6 UK clinical experts was convened in October 2005 and asked to provide consensus opinion about a range of clinical scenarios (including the appropriateness of the comparator) and resource utilisation representative of national practice. The choice of invited attendees was designed to represent national practice for the UK as a whole. In addition, two further clinical experts (Prof. Chris Boshoff, Medical Oncologist, and Dr. Tova Prior, Clincial Oncologist, both practicing at University College Hospital London) were asked to provide validation on assumptions not covered by the expert panel.

Table 15 Assumptions and Justification

Subject	**Assumption**	**Justification**	**Source**
Radiotherapy treatment (1)	The radiotherapy HRGs (health related groups) listed in the NHS Reference costs that apply to this patient population and indication are those that include technical support	Patients in this population will be immobilised in a shell which corresponds with the NHS definition of technical support: *"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…" (NHS Data Dictionary & Manual)*	Expert advice was sought from a clinical oncologist (Dr Tova Prior)
Radiotherapy treatment (2)	The unit costs from the radiotherapy HRGs were assumed to apply to the radiotherapy regimen and/or number of fractions received by each patient as applicable. Where more than one HRG was available, a weighted average was applied.	In the absence of per fraction costing, it is reasonable to assume that the HRG unit costs apply to a whole course of treatment.	Based on the results of the UK Expert Panel.
Cetuximab acquisition	For each administration, wastage is included in the cost 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 is a conservative assumption to ensure that the cost of cetuximab is not under-estimated.	Based on the results of the UK Expert Panel.

Subject	**Assumption**	**Justification**	**Source**
Administration for RT patients (1)	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.	Expert opinion	Based on the results of the UK Expert Panel.
Administration for RT patients (2)	Contact time with the specialist was estimated to be approximately one session per week of approximately 15 minutes each, which did not vary by regimen.	Expert opinion	Based on the results of the UK Expert Panel.
Administration for ERT patients (1)	Cetuximab is administered within an outpatient setting.	The administration schedule for Cetuximab (as per the summary product characteristics) is once per week intravenously over a period of approximately one hour (two hours for the initial dose).	Cetuximab SPC
Administration for ERT patients (2)	Cetuximab administration costs are always in addition to the cost of the radiotherapy administration.	Radiotherapy administration is assumed to be one session of 15 minutes per week, therefore it is reasonably assumed that the administration schedules do not overlap for cost purposes.	Based on the results of the UK Expert Panel.
Administration for ERT patients (3)	Where applicable, extra outpatient administrations were included for ERT administrations.	As per the clinical trial protocol, 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.	Bonner et al

Subject	**Assumption**	**Justification**	**Source**
Treatment-emergent adverse events (1)	Only those adverse events identified as the most significant cost drivers, with respect to a combination of the frequency of occurrence and the intensity of resources required for treatment, were included in the cost analysis. The identified events were as follows: • 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 • Leukopenia, 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	The size of the adverse event dataset made analysis of every individual event prohibitive. The dataset reports 8,207 separate patient events across both treatment groups, comprising over 300 types of event by COSTART (coding system for thesaurus of adverse reaction terms) definition. Given that the above listed events account for approximately 64% of all patient events recorded in the database, it is assumed that the remaining other types of event (approximately 280 further reports in the database) are rare and that all clinically important events or treatment differentiating events are included.	Personal communication, Prof. Chris Boshoff, University College Hospital London.

Subject	**Assumption**	**Justification**	**Source**
Treatment-emergent adverse events (2)	For cost purposes, it was assumed that mucositis, stomatitis and dysphagia can be grouped together, and similarly acne was grouped with rash, and nausea was grouped with vomiting.	Given the size of the adverse events database, it was desirable to incorporate any simplifying assumptions that would not bias the analysis	Assumptions were validated by Prof. Chris Boshoff.
Treatment-emergent adverse events (3)	Event costs were based on the expected cost of the average episode for each type of event and severity grade, rather than the recorded duration of each event in the trial dataset.	To account for missing and censored end dates of events, an expected cost per event was a necessary and pragmatic solution. Estimation of the typical resource utilisation (likelihood of hospital admission, medication, procedures etc) of each event.	Based on the results of the UK Expert Panel.
Imaging	An expected cost of imaging is applied to each patient.	Additional cost categories deemed to be of importance for this patient population were included in the analysis. UK clinical expert opinion was sought to provide estimates of the types of scans performed and the typical frequency.	Based on the results of the UK Expert Panel.
Routine monitoring (1)	An expected cost of routine monitoring is applied to each patient..	Estimates of the frequency and duration of monitoring for patients within this population were required to realistically capture all aspects of treatment.	Based on the results of the UK Expert Panel.

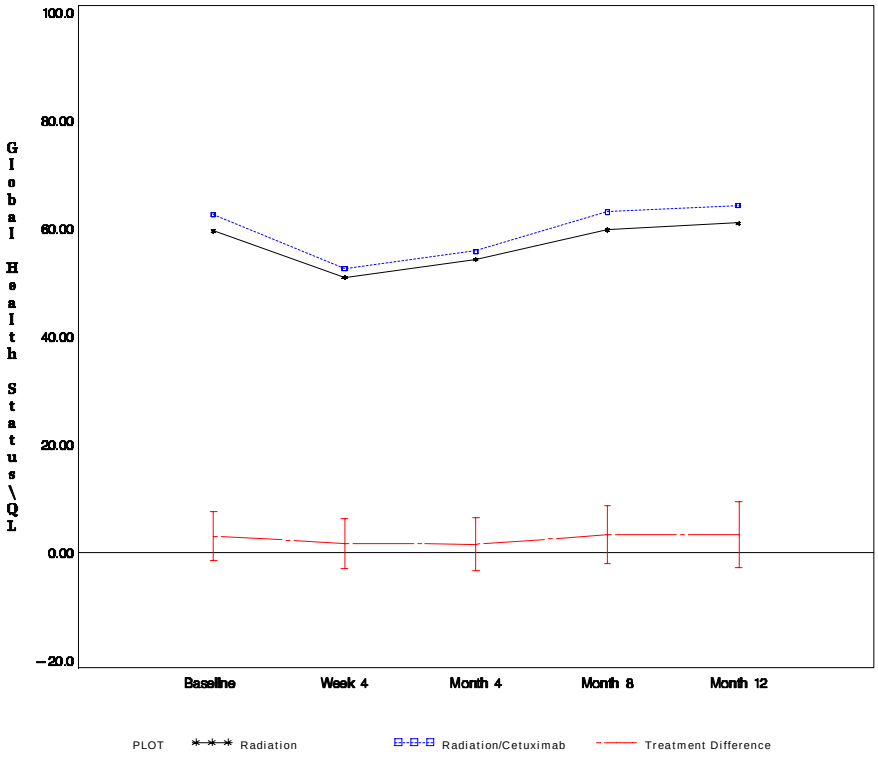
Subject	**Assumption**	**Justification**	**Source**
Routine monitoring (2)	Routine monitoring is assumed to occur from the end of the acute treatment phase until the time of disease progression.	Routine monitoring is assumed to cease at the time of progression to reflect a likely change in the pattern of care.	Based on the results of the UK Expert Panel.
Procedures (1)	The percutaneous endoscopic gastronomy (PEG) is the only procedure considered for cost purposes.	PEG was the only precautionary procedure identified by the UK Expert Panel as routinely performed in a significant proportion of patients.	Based on the results of the UK Expert Panel.
Procedures (2)	An expected cost of PEG is applied to each patient.	Additional cost categories deemed to be of importance for this patient population were included in the analysis. UK clinical expert opinion was sought to provide estimates of the frequency of PEG placement.	Based on the results of the UK Expert Panel.
Salvage/ Palliative care (1)	Salvage/palliative care is assumed to be administered at the point of disease progression.	Routine monitoring is assumed to cease at the time of progression to reflect a likely change in the pattern of care.	Based on the results of the UK Expert Panel.
Salvage/ Palliative care (2)	An expected cost of salvage/palliative care is applied to each patient.	Additional cost categories deemed to be of importance for this patient population were included in the analysis.	Based on the results of the UK Expert Panel.

Subject	**Assumption**	**Justification**	**Source**
Salvage/ Palliative care (3)	The proportion of patients receiving each type of secondary therapy is assumed to be as reported in the clinical trial.	Summary information on secondary anticancer therapies received was reported for 212 (RT) and 208 (ERT) patients at the time of the data cut-off in the pivotal trial. Some patients had not progressed at this time-point, so the data on secondary anticancer therapies received is not fully mature. However, the trial data was considered to be the best data source available and it was used in the economic model exactly as reported from the trial.	Bonner et al
Overall and progression-free survival	OS and PFS dates were estimated to replace censored survival dates in the trial dataset, since a significant number of patients were alive at the end of the trial period. A statistical cure model was used to perform the extrapolation.	Multiple statistical models for extrapolation of censored data were explored. Based on standard tests, the cure model was found to be the most appropriate of the alternatives. Two additional analyses are provided, one using an alternative extrapolation (Weibull) and the other using only the trial PFS and OS data (with no imputation).	A full description of the statistical cure model used to extrapolate censored data is contained in Technical Appendix 2

Health state utilities:

The pivotal trial included two quality of life instruments: the EORTC QLQ-C30 and the EORTC QLQ H&N35. Results for the two instruments indicate that ERT does not impact negatively on patient QoL (see Figure 4).

Figure 4 Plot of survival curves stratified at baseline EORTC QLQ-C30 global health status/QoL scores evaluable for QLQ-C30 population[34]



However, neither instrument produces a utility value and a method is not available for mapping the EORTC QLQ-C30 to a utility instrument. It was decided to conduct a health state valuation study in parallel to the economic evaluation in order to retrospectively estimate utility values in the pivotal study. This study is briefly described below and further details are available in Technical Appendix 3.

The utility valuation was based upon ratings of hypothetical health states designed to represent patient experiences of adverse side effects arising from their treatment for locally advanced SCCHN and post–treatment outcomes. These health states were assessed using the EQ–5D questionnaire. Due to

ethical and practical considerations, it was not desirable to directly interview patients concerning their views on the health states in the study. It was therefore decided to use the nurses who work at specialist oncology centres as patient proxies. 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. The recruitment of respondents and interview field work for the study was conducted by Silverfern Research International in Sept - Oct 2005.

Seven health states were developed to represent the acute stage of treatment and two further health states covered the post-acute treatment phase. These are shown in **Table 16**.

Table 16 Health state utilities

Variable	Utility Value in base case
Acute phase health states	
A - General In-Treatment	0.659
B - Mucositis/dysphagia/stomatitis grade 3 or 4	0.062
C - Mucositis/dysphagia/stomatitis grade 2	0.608
D - Nausea & vomiting grade 3 or 4	0.108
E - Nausea & vomiting grade 2	0.573
F - Acne/rash grade 3 or 4	0.226
G - Haemotological grade 4	0.101
Post-treatment health states	
J - Locoregional control	0.862
K - Progressive disease	0.129

The domains of each of these seven health states described various severities of different side effects based on National Cancer Institute (NCI) common toxicity criteria (CTC) system grading system (http://ctep.cancer.gov/reporting/ctcnew.html). The seven health states were:

- less than or equal to grade 1 nausea/vomiting and mucositis / stomatitis / dysphagia
- grade 2, nausea/vomiting
- grade 3 or 4 nausea/vomiting
- grade 2 mucositis / stomatitis / dysphagia

- grade 3 or 4 mucositis / stomatitis / dysphagia
- less than or equal to grade 1 nausea/vomiting and mucositis with the addition of grade 3 and 4 acne/rash
- less than or equal to grade 1 nausea/vomiting and mucositis with the addition of grade 3 and 4 haematological toxicity

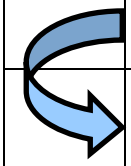
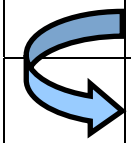
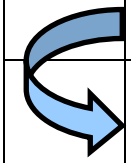
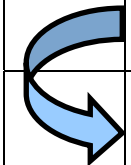
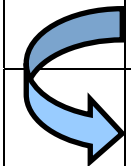
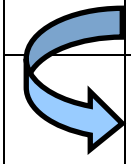
The following assumptions were applied to the Health state utilities and can be found in Table 17 below.

Table 17 Assumptions on Health state Utilities

Assumption	Justification	Source
1. Health states were stratified chronologically into either acute phase or post-treatment states.	The vast majority of treatment-emergent adverse events do not persist far beyond the acute phase. In addition, the assumptions that patient quality of life (QoL) can be differentiated according to adverse status and disease status, in the acute phase and post treatment respectively, were validated.	Clinical expert opinion (Prof. Chris Boshoff)
2. Patient QoL is best represented by ranking the health states into a hierarchy with the worst health state taking precedence, followed by the second-worst and so on.	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. The 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.	Based on the results of the UK Expert Panel.
3. With the exception of health state A (general in-treatment), where time in an acute phase health state caused the total time to overrun the allocated total time in the acute phase, the full duration in the health state was applied.	This assumption ensures that the economic model does not underestimate the QoL implications of an acute phase adverse event.	Validated by the UK Expert Panel.
4. Late toxicity health states H (peripheral neuropathy) and I (ototoxicity) do not apply to the analysis.	Although health states H and I were included in the utility valuation study, the UK Expert Panel indicated that these health states do not apply to RT or ERT patients.	Based on the results of the UK Expert Panel.

Each patient's adverse events were consolidated to assess which health states they would have spent time in and on how many occasions. Using this gathered information on each patient, utilities were assigned for the acute phase according to the following algorithm found below in Table 18.

Table 18 Algorithm of Health state utilities

	If a patient experienced at least one health state B adverse event (**mucositis/ dysphagia/ stomatitis grade 3 or 4**), then they were allocated the utility value for this health state for the average duration of this event. Otherwise;
	If a patient experienced at least one health state G (**haematological grade 4**) 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 (**nausea & vomiting grade 3 or 4**) 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 (**acne/ rash grade 3 or 4**) 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 (**nausea & vomiting grade 2**) 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 (**mucositis/ dysphagia/ stomatitis grade 2**) 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 **(general in-treatment**) for all remaining acute phase time.

83. **Why was this particular type of model used?**

Individual patient-level modelling was chosen as the best modelling option in order to take advantage of a rich clinical dataset that recorded all relevant clinical efficacy (overall and progression-free survival) and safety endpoints. Due to the excellent individual clinical data, robust statistical extrapolation of survival data was reasonably assumed to be of superior value than, say, extrapolation of survival using Markov modelling and a 'per cycle' risk of failure. Similarly, the vast majority of treatment costs occur within the trial period, meaning that Markov modelling would add little value to the costs observed by the trial dataset (Bonner *et al*., 2006/EMR 62 202-006).

84. **What was the justification for the chosen structure/how was disease progression represented?**

The chosen model structure – delineation between acute phase and post-treatment – is sufficient to cover the relevant clinical endpoints. Expert opinion (Prof. Chris Boshoff, and the UK Expert Panel) validated this delineation and indicated that – for cost and patient QoL purposes – there is no significant difference between locoregional control and stable disease. Disease progression is represented by an individual date of progression (whether actual or imputed), which causes the individual to move from health J to K and a shift in the pattern of care.

85. **Is this consistent with a coherent and currently accepted theory of disease progression?**

As noted above, the assumption within the economic model regarding disease progression is in line with the generally accepted treatment and progression pathway associated with this disease and was validated by clinical expert opinion.

86. **What were the sources of information used to develop and inform the structure of the model?**

The structure of the model, with regards to timings, costs and transition between health states, is based on the pivotal clinical trial (Bonner *et al*., 2006/EMR 62 202-006) and clinical expert opinion.

87. **What other structures/measures of disease progression could have been used to inform the structure of the model? Why were they rejected?**

As noted above, further stratification of disease progression was considered with regards to locoregional control, stable disease and progressive disease. However, clinical expert opinion indicated that dividing the pre-progression phase into locoregional control and stable disease, would have been of little practical value in terms of differentiating patient costs and QoL.

88. **Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?**

It is assumed that the essential features of the condition relevant to the decision model are the adverse event status during the acute phase, disease progression and overall survival. Each of these elements is captured by the economic model.

89. **For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?**

The economic evaluation does not include a discrete time model and therefore this is not applicable.

90. **If appropriate, was a half-cycle correction used in the model? If not, why not?**

The economic evaluation does not include a discrete time model and therefore this is not applicable.

91. **Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and why are they justified? In particular what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?**

Yes, costs and outcomes are extrapolated beyond the trial period. The assumptions that underpin this extrapolation are described within the methods of the statistical cure model (Technical Appendix 2) used to impute censored values of progression-free and overall survival.

3.2.6.2 Non-model-based economic evaluations

- *Was the evaluation based on patient-level data from a clinical trial or trials?*

Yes, the evaluation was based on the patient-level dataset of the pivotal clinical trial (Bonner *et al*., 2006/EMR 62 202-006).

- *Provide details of the clinical trial, including the rationale for its selection.*

The pivotal trial (Bonner *et al*., 2006/EMR 62 202-006) is a multinational, randomised study comparing radiotherapy alone with radiotherapy plus cetuximab, in the treatment of locoregionally advanced squamous-cell carcinoma of the head and neck. This trial was selected as it is the only one of relevant to this submission.

- *Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?*

No, data was not complete for all patients. Where data was missing, the methods and assumptions used for dealing with missing data are described above in the response to question 82.

- *Were relevant data collected for all patients in the trial? If data were collected for a subgroup of patients in the trial, how were the data extrapolated to a full trial sample?*

The economic model uses such data as were available for the full trial sample (e.g. PFS, OS, adverse events, study drug use, radiotherapy use, etc). Where data were censored (e.g. PFS and OS dates), imputation methods were applied (as described above). However, it was not the case that data for a subgroup of patients in the trial was extrapolated to the full trial sample.

3.2.7 Evidence

3.2.7.1 Clinical evidence

Where relevant, answers to the following questions should be derived from and consistent with, the clinical evidence section of the submission. Cross references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

It is worth restating that the clinical data used in the economic evaluation is the individual patient level data recorded in the clinical trial dataset (Bonner *et al*., 2006/EMR 62 202-006) and extrapolation of censored data, not the overall clinical results as presented in Section 2. Please refer to Section 2 for these results, which provide indicative trends but do not represent the health outcomes results estimated by the economic evaluation.

92. **How was the baseline risk of disease progression estimated (also state which treatment strategy represents the baseline)?**

Disease progression was based on the observed data from the clinical trial (Bonner *et al*., 2006/EMR 62 202-006) where it is recorded, and imputed via the statistical cure model where it is not.

93. **How were the relative risks of disease progression estimated?**

Please refer to the answer to question 92.

94. **Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?**

Yes, intermediate outcome measures are linked to final outcomes throughout the analysis. Every patient's duration of overall survival (whether actual or imputed) was allocated into health states, according to adverse events status in the acute phase and disease status post-treatment. As noted above, the assumptions used to allocate overall survival to health states were validated by clinical experts.

95. **Were the health effects of adverse events associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?**

Yes, the adverse effects of cetuximab are considered in the economic evaluation.

96. **Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?**

No, all clinical parameters (progression-free, overall survival, adverse events, health state utilities) were derived from the pivotal clinical trial (Bonner *et al*.,

2006/EMR 62 202-006) itself, the utility valuation study or estimated via statistical extrapolation where data was censored. Expert opinion was used to validate clinical assumptions (see the response to question 82) but not to provide values for clinical parameters.

97. **What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?**

All model assumptions (including those underpinning clinical parameters) are outlined in the response to question 82.

3.2.7.2 Measurement and valuation of health

98. **Which health benefits were measured and how was this undertaken?**

As noted above, the health effects measured were:

- Adverse events for each patient, derived from the clinical trial dataset (Bonner *et al.*, 2006/EMR 62 202-006).
- Progression-free and overall survival, measured individually for each patient (imputed where censored via the statistical cure model).

99. **Which health benefits were valued? How and why were these values selected? What other values could have been used instead?**

As noted above, the health state utilities were valued via the utility valuation study. Utility values for the health states were estimated from a study of oncology nurses in the UK using the EQ-5D, which is weighted according to the social preferences of the UK population. A full description of the health state utility study is included within Technical Appendix 3. The EQ-5D was chosen as a generic non-disease-specific instrument preferred as outlined in the Guide to the Methods of Technology Appraisal.

The EORTC QLQ-C30 results were not used in the economic evaluation because it is not a preference-based measure of health-related quality of life and no method was available for converting QLQ-C30 results to utilities. A

second barrier to using the trial-based quality of life data is that the QLQ-C30 questionnaire was completed for the first 12 months only.

While no statistical analyses has been carried out to compare the consistency between the EQ-5D based utility valuation study and the QLQ-C30 results from Bonner *et al.*, 2006/EMR 62 202-006, results presented do suggest consistency. The utility scores for RT and ERT at the end of the acute phase of treatment are estimated to be 0.03665 and 0.033254 respectively. The difference of 0.0034 is extremely small, indicating little or no difference in the quality of life of patients in the acute phase of treatment. This is consistent with the results of the QLQ-C30 data, as shown in **Figure 4** (question 82).

100. **Were health benefits measured and valued in a manner that was consistent with NICE's Reference Case? If not, which approach was used?**

Clinical evidence was based on a pivotal clinical trial (Bonner *et al.*, 2006/EMR 62 202-006), not on systematic review as in the Reference Case. A systematic review was not necessary in this case as the pivotal trial is the only head-to-head, randomised controlled trial available. No relevant clinical evidence was knowingly omitted.

In line with the Reference Case, health state utilities were valued using a non-disease-specific instrument (EQ-5D). The study derived health state valuations from the patient perspective, but due to ethical considerations the EQ-5D was completed by UK oncology nurses as a proxy respondent group. Refer to the response to question 82 for full details.

101. **Which possible (dis)health benefits were excluded from the evaluation (for example, adverse events of treatment)?**

No (dis)health benefits were excluded from the analysis.

102. **If health benefits were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?**

Health effects were expressed as QALYs.

3.2.8 Resource identification, measurement and valuation

103. **What resources were included in the evaluation (the list should be comprehensive and as disaggregated as possible)?**

The list of resources included in the analysis, as noted above in question 82, was as follows:

- Radiotherapy treatment
- Cetuximab acquisition
- Treatment administration for RT patients
- Treatment administration for ERT patients
- Treatment of adverse events (including hospitalisations, concomitant medications and procedures)
- Imaging
- PEG
- Routine monitoring post-treatment
- Salvage/palliative care post-progression

104. **How were the resources measured?**

See the response to question 82 for further information on assumptions regarding the measurement of resources.

Radiotherapy treatment:

The regimen of radiotherapy and number of fractions received by each patient was recorded by the clinical trial dataset (Bonner *et al.*, 2006/EMR 62 202-006).

Cetuximab acquisition:

The actual dose of cetuximab administered to each patient was recorded by the clinical trial dataset.

Treatment administration for RT patients:

Administration of radiotherapy is set according to local practice. The UK Expert Panel indicated that although RT is administered on a daily basis, contact time with a specialist occurs approximately once per week for about 15 minutes. Therefore separate outpatient visits are only included for these weekly sessions.

Treatment administration for ERT patients:

Cetuximab administration is assumed to be delivered in an outpatient setting (see question 82). One outpatient visit is allocated for each dose administered as reported in the clinical trial dataset.

Treatment of adverse events:

The individual events experienced by patients are reported in the clinical trial dataset. All resource parameters (likelihood of hospitalisation, concomitant medications and procedures) used to calculate the expected cost of each adverse event, are derived from the UK Expert Panel.

Imaging:

The likelihood that patients receive each type of scan and their frequency were estimated by the UK Expert Panel. These values are used to calculate

an expected cost of imaging per patient per year dependent on individual overall survival.

Precautionary PEG:

The likelihood that patients have a precautionary PEG inserted was estimated by the UK Expert Panel. This value is used to calculate an expected cost of PEG per patient per year dependent on individual overall survival.

Routine monitoring:

The frequency of routine monitoring visits was estimated by the UK Expert Panel. These values were used to calculate an expected cost of routine monitoring per patient, dependent on individual progression-free survival.

Salvage/palliative care post-progression:

The expected cost of salvage/palliative care is applied as a one-shot cost at the point of progression for each patient. The proportion of patients receiving each type of secondary therapy is as reported in the clinical trial report, which is used to calculate a weighted average overall cost. The individual costs of each secondary therapy are as set out in question 82.

105. **Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?**

As noted above in Section 3.2.7.1, disease progression was based on the observed data from the clinical trial (Bonner *et al.*, 2006/EMR 62 202-006) where it is recorded, and imputed via the statistical cure model where it is not. Where available, resources were measured via the clinical trial dataset. Where resource utilisation was not recorded by the clinical trial, they were estimated via the UK Expert Panel (please see the response to question 104).

106. **What source(s) of information were used to value the resources?**

The resources were valued using standard UK unit cost sources.
Radiotherapy treatment: Radiotherapy was valued using the appropriate HRG unit costs as listed in the NHS Reference Costs.

Cetuximab acquisition: The cost of a vial of cetuximab was sourced from BNF 50.

Treatment administration for RT patients: The outpatient visit unit cost is sourced from the appropriate outpatient specialty code in the NHS Reference Costs.

Treatment administration for ERT patients: The outpatient visit unit cost is sourced from the appropriate outpatient specialty code in the NHS Reference Costs.

Treatment of adverse events: Hospitalisations were valued according to the appropriate HRG unit cost from the NHS Reference Costs. Similarly, procedure costs were also drawn from the Reference Costs. Unit costs of concomitant medications were derived from BNF 50.

Imaging: The unit costs of each type of scan were derived from the NHS Reference Costs.

Preventative PEG: The unit cost of PEG insertion was sourced from the appropriate HRG in the NHS Reference Costs.

Routine monitoring: The outpatient visit unit cost is sourced from the appropriate outpatient specialty code in the NHS Reference Costs.

Salvage/palliative care post-progression: Each of the secondary therapy alternatives was valued as follows.

- Community nursing unit costs were derived from the NHS Reference Costs.
- The cost of salvage surgery was sourced from an inpatient HRG unit cost in the NHS Reference Costs.
- The cost secondary radiotherapy was assumed to be equal to the mean cost of radiotherapy treatment in the RT group.
- The cost of secondary systemic therapy was valued as a single course of cisplatin chemotherapy (unit cost from BNF 50).

107. **What is the (anticipated) acquisition cost excluding VAT of the intervention(s)?**

The acquisition cost of cetuximab (as listed on BNF 50) is £136.50 per 100 mg vial. In the economic evaluation, each patient dose is rounded up to the

nearest whole vial and the full cost absorbed. The dosage regimen of cetuximab is an initial loading dose of 400mg/m^2 in week one followed by subsequent doses of 250mg/m^2 for weeks 2-8. Assuming a body surface area range of 1.6m2 to 1.8m2, the drug cost per whole course of therapy is £4,778 - £5,873. The average drug cost per patient in the economic model is £5,489.

108. **Were the resources measured and valued in a manner consistent with the Reference Case? If not, how and why do the approaches differ?**

Resources were measured and valued in a manner consistent with the Reference Case. The resources measured were those under the control of the NHS and they were valued from the perspective of the NHS.

109. **Were resource values indexed to the current price year?**

In all cases, the most recently published (at the time of analysis) unit cost source was used, therefore it was not necessary to index costs to current price year.

110. **Provide details and a justification for any assumptions that were made in the estimation of resource measurement and valuation.**

All modelling assumptions are included in the response to question 82.

3.3 Analysis of data

3.3.1 Time preferences

111. **Were costs and health benefits discounted at the rates specified in NICE's Reference Case?**

Yes, both costs and health effects were discounted to present value at 3.5% per annum as specified in the Reference Case.

3.3.2 Non-linearity

112. **Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.**

Probabilistic sensitivity analysis (PSA) was not undertaken because individual patient outcomes were available. Instead, a stochastic sensitivity analysis was performed by the method of bootstrapping. This method explores uncertainty around individual patient variability and allows the presentation of the results by a cost-effectiveness acceptability curve (CEAC). Moreover, since each sample is constructed by the estimated individual patient result, this method does not require assumptions associated with probability distributions fitted to model parameters.

3.3.3 Statistical analysis

113. **How were rates or probabilities based on intervals transformed into (transition) probabilities?**

Transitions between health states were based on actual observations rather than transition probabilities where such data was recorded. Where data were censored, transitions from health state J (locoregional control/stable disease) to health state K (progressive disease) and from either state to death was imputed via a statistical cure model. A full description of the rationale and methods of the cure model is included in Technical Appendix 2.

114. **Is there evidence that (transition) probabilities should vary over time for the condition at hand? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.**

Given that the primary aim of treatment is curative, it is important that the imputation of dates of disease progression and death account for the proportion of patients who may never progress (i.e. are 'cured'). With this in mind, the transition between the post-treatment health states is moderated by an implicit 'cure fraction' within the statistical cure model. A full description of

the rational and methods of the cure model is included in Technical Appendix 2.

3.3.4 Validity

115. **Describe the measures that have been taken to validate and check the model.**

All model resource use assumptions were validated by the UK Expert Panel.

The cure model used to impute censored PFS and OS dates is validated in several ways. Firstly, an alternative (Weibull) model is provided for comparison, which shows that the cure model results are conservative towards ERT. Secondly, the results of the cure model were compared with the results of a STATA® (StataCorp LP, Texas) command which estimates the area under the curve (AUC) based on the observed data and using an extrapolation (exponential) of the survival curves if necessary. The results from this command are very similar to the results of the cure model. Whilst this is essentially a coincidental outcome, it shows that the cure model results are at least more conservative or consistent with alternative methods.

3.4 Results

3.4.1 Base-case result and PSA

116. **What was the base-case result (e.g. costs, QALYs and incremental cost per QALY) and was it based on PSA?**

The base-case result is calculated by modelling individual patient cost and health outcomes over a lifetime (clinical trial period and extrapolated survival where data were censored). A stochastic sensitivity analysis was performed to explore uncertainty around individual patient outcomes by sampling with replacement. The results of this analysis are presented in the response to question 117.

Cost result:

Table 19 presents the distribution of how cost is accumulated by patients moving through the model.

Table 19 Costs by model phase

Regimen	Acute phase	Locoregional control	Progressive disease	Expected total
RT	£4,434.88	£1,628.76	£1,131.34	**£7,194.99**
ERT	£10,875.07	£1,867.58	£1,077.89	**£13,820.55**

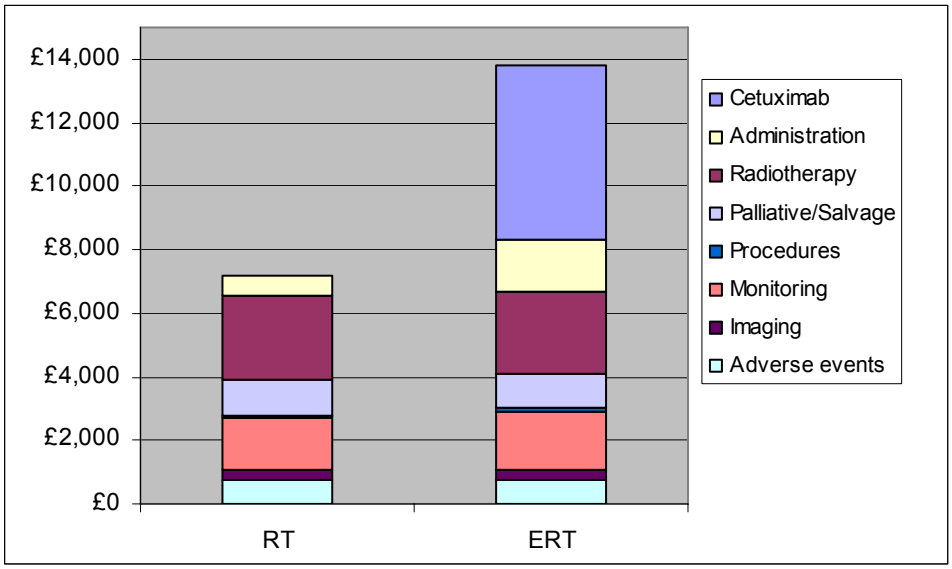
Most of the cost in the model is incurred within the first 5 years of therapy, and in particular for the ERT regimen in the acute phase. Imaging and routine monitoring cost are accrued during the first three and four years respectively. Palliative care is assumed to be administered at the point of disease progression.

The economic model estimates that ERT is associated with a higher expected cost per patient than RT, with an incremental cost of approximately £6,626. The expected cost values per patient estimated by the economic model are presented in **Table 20**. The key driver of the cost difference is the cost of cetuximab acquisition and subsequently the administration cost, with all other cost categories being comparable between the two treatment groups. **Figure 5** presents a comparison of the cost components.

Table 20 Cost results

Resource	RT	ERT	Increment
Study drug	£0	£5,489	**£5,489**
Radiotherapy	£2,661	£2,597	**-£63**
Therapy administration	£609	£1,621	**£1,012**
Adverse event costs	£760	£762	**£2**
Imaging	£293	£293	**£1**
Monitoring	£1,629	£1,868	**£239**
Procedures	£112	£112	**£0**
Palliative	£1,131	£1,078	**-£53**
Total	**£7,195**	**£13,821**	**£6,626**

Figure 5 Cost components



Health outcomes result:

The economic model estimates that patients treated with ERT gain on average a total of 3.8532 QALYs compared to 2.8162 QALYs for those treated with RT over the course of a full lifetime.

Table 21 presents the QALYs gained by phase of the model.

Table 21 QALYs gained by model phase

Regimen	Acute phase	Locoregional control	Progressive disease	Expected total
RT	0.0366	2.6253	0.1543	2.8163
ERT	0.0333	3.7118	0.1082	3.8532

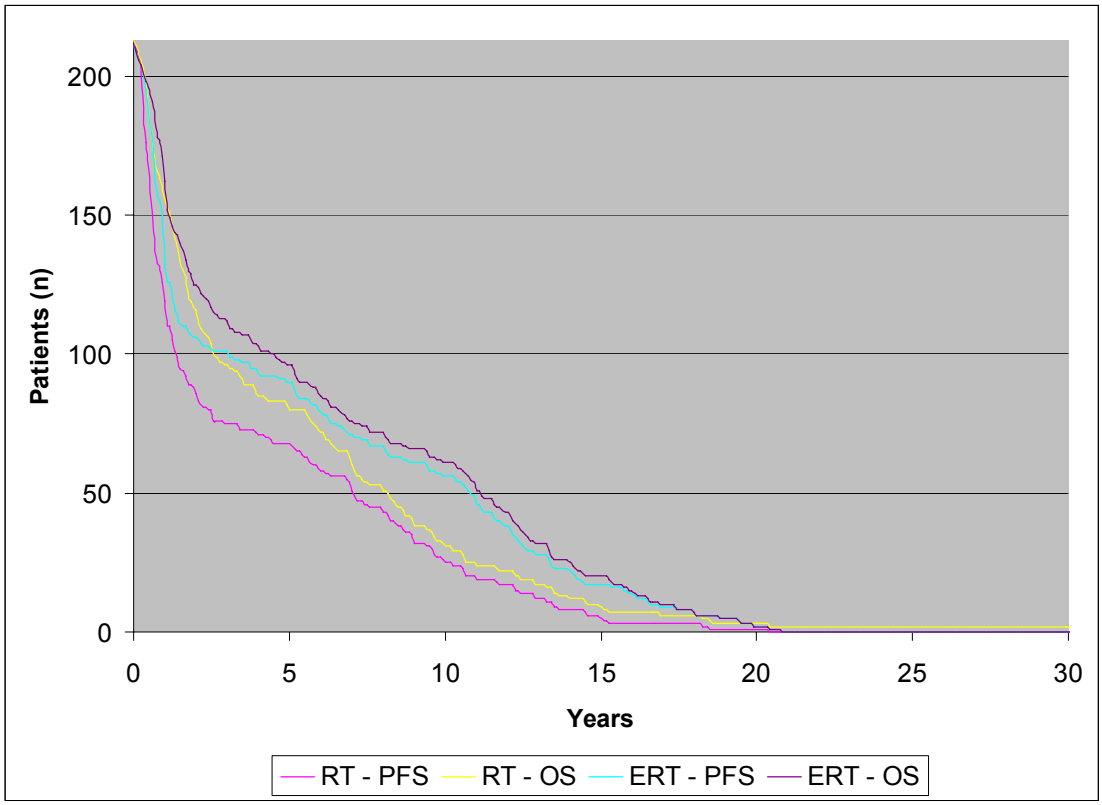
Table 22 summarises the health benefits of the two treatments in terms of QALYs, overall survival (OS) and progression free survival (PFS).

Table 22 Health outcomes results

	RT	ERT	Increment
QALYs	2.8162	3.8532	1.0369
Overall survival	4.0604	4.9475	0.8866
Progression-free survival	3.1850	4.4432	1.2582

Extrapolation of censored survival estimates are imputed into the economic model via the statistical cure model. **Figure 6** presents the survival curve of progression free survival and overall survival for both arms. Figure 6 reinforces how minor differences in the utility values are not the key driver of model results, but the efficacy data supporting locoregional control and overall survival.

Figure 6 Overall survival and progression-free survival curves



Incremental cost-effectiveness ratios result:

In the base case analysis, ERT patients are estimated to gain 1.26 QALYs extra and have an incremental cost of £6,626 compared to RT patients. This translates into the following incremental cost effectiveness ratio (ICER) of ERT in comparison with RT:

- **£6,390 per QALY gained over the expected patient lifetime**
- **£7,473 per extra life year gained**
- **£5,266 per extra progression-free life year gained**

Table 23 presents the range of ICERs.

Table 23 Incremental cost-effectiveness ratios

Analysis	Lifetime
Incremental cost per QALY gained	£6,390
Incremental cost per LY gained	£7,473
Incremental cost per PFLY gained	£5,266

117. **Please provide cost-effectiveness acceptability curves and scatterplots on cost-effectiveness quadrants.**

In order to address uncertainty around the observed cost and effect values of the model cohort, a stochastic sensitivity analysis was performed on the lifetime cost utility analysis. By the method of bootstrapping, individual patient cost and health outcomes estimates were sampled with replacement. Bootstrapping is a procedure that estimates an empirical sampling distribution for the statistic of interest, in this case the expected costs and effects. It involves the random sampling of patients where replacement of individual outcomes is allowed to provide a different expected average cost and effect result for each bootstrap sample. Repeating this process a large number of times generates a vector of bootstrap replicates.

In this analysis 2,000 samples were obtained from the observed estimates in both the ERT and RT groups. The bootstrap summary results are presented in **Table 24**. The bootstrap summary presents the mean of the empirical distribution of cost-effectiveness of ERT vs. RT. The cost-effectiveness acceptability curve in **Figure 7** presents the probability that ERT is cost-effective compared to RT across different threshold values. **Figure 8** presents the cost-effectiveness plane with the 2,000 ICER values plotted.

Table 24 Bootstrap summary

	Cost (£)	QALYs
Observed values		
RT	7194.98	2.816276
ERT	13,820.55	3.853187
Incremental	6,625.561	1.036912
Bootstrap summary		
RT	7,046.201	3.269301
ERT	13,697.51	4.429158
Incremental	6,651.306	1.159857
Standard error of incremental values	206.552	0.359721
95% Bias-Corrected Lower Confidence Limit	6,155.11	0.23
95% Bias-Corrected Upper Confidence Limit	6,973.75	1.652462

Figure 7 Cost-effectiveness acceptability curve

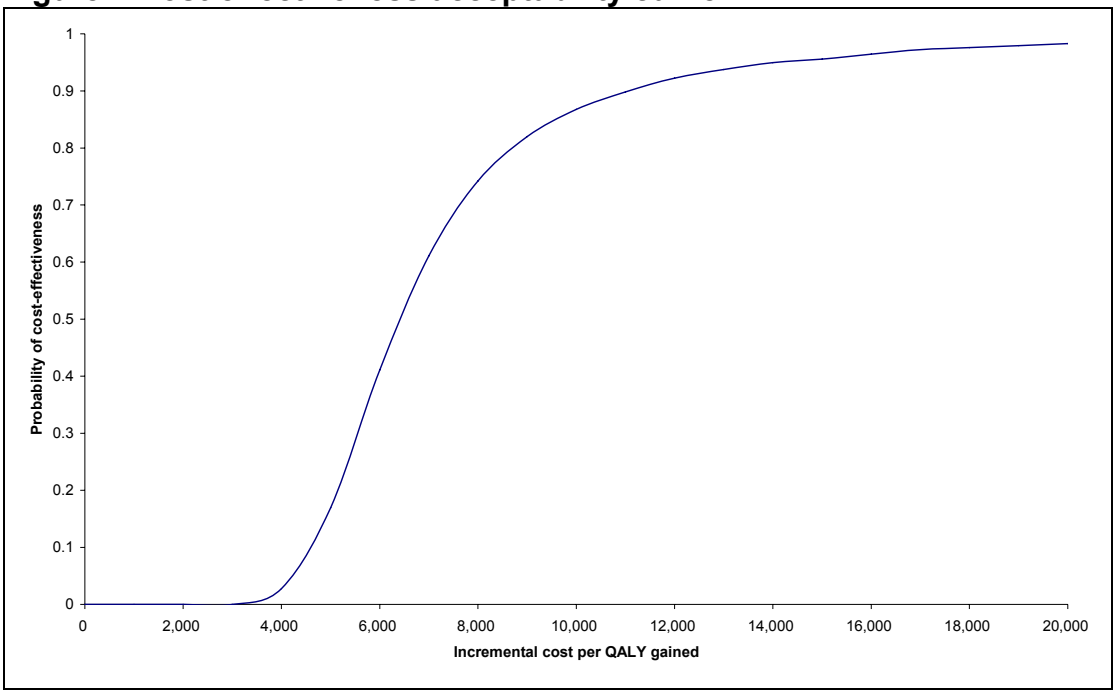
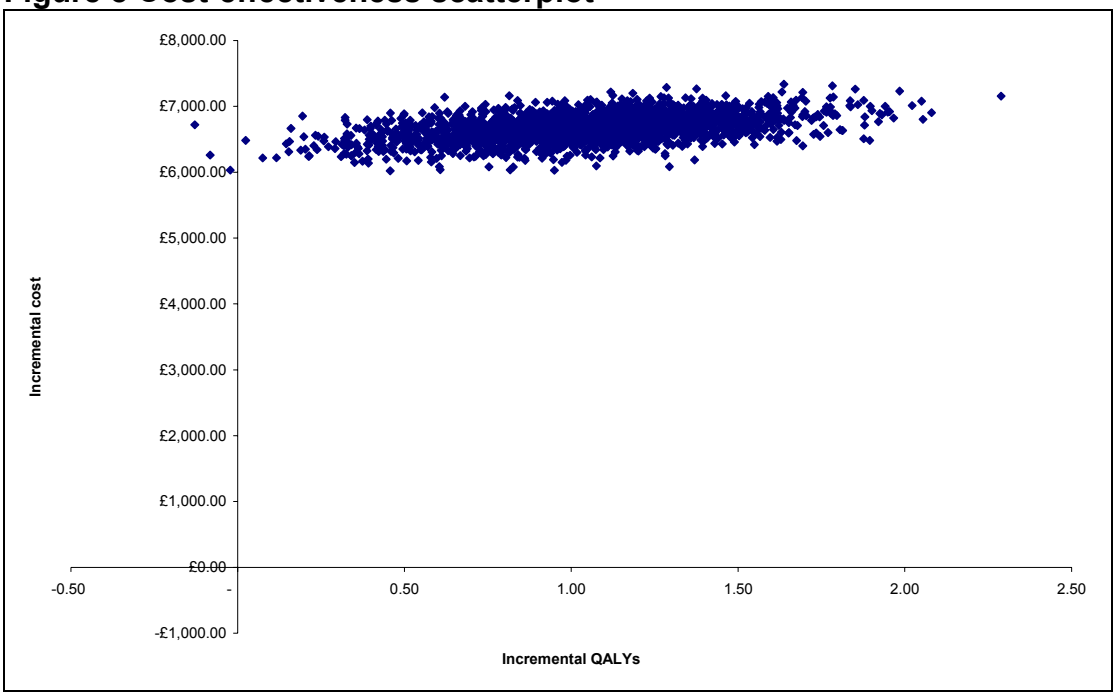


Figure 8 Cost-effectiveness scatterplot



118. **Were results reported for different subgroups of patients? If so, what were the results for them?**

No subgroup analyses were performed.

3.4.2 One-way/multiway sensitivity analysis

Sensitivity analysis should be conducted over a plausible range of prices for technologies whose final price/acquisition cost has not been confirmed.

119. **Which variables were subject to sensitivity analysis?**

Table 25 presents the extensive one-way sensitivity analysis completed.

Table 25 One-way sensitivity analysis

Sensitivity analysis	Description of sensitivity analysis and variable(s) tested	Values used in sensitivity analysis	ICER (£/QALY)	Change (£/QALY)
	Base case result		6389.71	
A	No discounting	0% (costs), 0% (outcomes)	4905.20	-1484.51
B	Outcomes not discounted	3.5% (costs), 0% (outcomes)	4858.95	-1530.76
C	Decrease discount rate to 2.5%	2.5 (costs), 2.5% (outcomes)	5936.62	-453.09
D	Increase discount rate to 5%	5% (costs), 5% (outcomes)	7109.71	720.01
E	Increase discount rate to 10%	10% (costs), 10% (outcomes)	9821.80	3432.09
F	Remove radiotherapy administration cost	No specialist visits allocated to RT admin	6386.64	-3.06
G	Double cost of mucositis treatment	£189.45 (grade 2), £614.36 (3), £6,071.39 (4)	6424.77	35.07
H	Halve cost of mucositis treatment	£47.36 (grade 2), £153.59 (3), £1,517.85 (4)	6372.17	-17.53
I	Double cost of nausea & vomiting treatment	£161.35 (grade 2), £666.59 (3), £2,198.12 (4)	6382.12	-7.58
J	Halve cost of nausea & vomiting treatment	£40.34 (grade 2), £166.65 (3), £549.53 (4)	6393.50	3.79
K	Set all acute health state utilities as general in-treatment	0.659 (health states B, C, D, E, F & G)	6380.20	-9.51
L	Set all acute health state utilities to worst acute utility	0.062 (health states B, C, D, E, F & G)	6369.91	-19.79
M	Set length of event to 10 days for health state B	10 days (health state B)	6377.43	-12.28
N	Set length of event to 20 days for health state B	20 days (health state B)	6377.62	-12.08
O	Set length of event to 10 days for health states B & D	10 days (health state B), 10 days (health state D)	6377.47	-12.24
P	Set length of event to 20 days for health states B & D	20 days (health state B), 20 days (health state D)	6377.55	-12.16
Q	Set length of event to 10 days for all acute health states	10 days (health states B, C, D, E, F & G)	6382.34	-7.37
R	Set length of event to 20 days for all acute health states	20 days (health states B, C, D, E, F & G)	6381.57	-8.14
S	Halve increment between locoregional control and progressive disease utility	0.67875 (health state J), 0.31225 (health state K)	8948.74	2559.04
T	Equalise locoregional control and progressive disease utilities to the average	0.4955 (health state J & K)	14926.76	8537.05
U	Analysis Timeframe: No imputation	Use unextrapolated trial data.	19950.99	13561.28
V	Analysis Timeframe: 10 years	Cap economic analysis after 10 years.	9207.51	2817.80
X	Survival analysis: Weibull model	Use Weibull model to extrapolate trial survival	5868.18	-521.52

120. **What were the main findings of the sensitivity analysis?**

The analysis demonstrates that the model is not sensitive to change when assessing radiotherapy administration cost, changes to the costs of adverse events, changes to the utility rewards of each state or changes to the time in the health states.

Relatively large variability was observed when the timeframe of the analysis changed from lifetime to the trial period only (with no imputation), resulting in an ICER of £19,951 per QALY gained. PFS and OS were significantly higher on ERT than RT at the end of the trial period, so truncating the analysis at this time point obviously under-estimates the benefit of ERT. Nonetheless ERT, even under such extreme modelling conditions is still of acceptable cost-effectiveness at £19,951 per QALY gained.

Significant variability in the ICER occurred when the timeframe was reduced from lifetime to 10 years and when the discounting rate increased from 3.5% to 10%.

Several parametric models were investigated for the purpose of extrapolating censored trial data. The cure model was found to be the most conservative and consistent model to use (see Technical Appendix 2). However, for ease of comparison a Weibull extrapolation was also performed. The Weibull model resulted in a cost per QALY gained of £5,868. This is a modest improvement in the ICER in favour of ERT compared to the base case (using the cure model extrapolation). Thus the use of the cure model is shown to be conservative towards ERT.

121. **Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?**

A sensitivity analysis associated with the structure of the model was not performed. As a trial-based modelling approach was adopted, structural

uncertainties are less important than would be the case with other approaches to modelling.

3.4.3 Interpretation of economic evidence

122. **Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ and why should the results in the submission be given more credence than those in the published literature?**

There are no published economic evaluations of ERT in SCCHN with which to compare the results.

123. **Is the economic evaluation relevant to all groups of patients who could potentially use the technology?**

The purpose of the economic evaluation is to estimate the cost-effectiveness of (ERT) compared to RT in the treatment of locally advanced head and neck cancer for those patients who are considered inappropriate for chemoradiotherapy but suitable for radiotherapy.

The economic evaluation is not relevant for patients who are suitable for chemoradiotherapy. The relevant economic evaluation in that case would be a comparison between ERT and chemoradiotherapy. No clinical trials have been conducted comparing ERT versus chemoradiotherapy in locally advanced SCCHN, so it is difficult to reliably perform such a comparison.

124. **What are the main strengths and weaknesses of the evaluation? How should these affect the interpretation of the results?**

The main strength of the analysis is the clinical trial upon which the economic model is closely based. The Bonner study is one of the largest trials conducted in this disease area and demonstrates significant benefit of ERT on locoregional control and overall survival (as well as other key end-points), without significantly exacerbating the toxicities related to radiotherapy.

The economic model is relatively simple. Costs are extremely similar for the two arms except for the additional cost of cetuximab, and the differences in health outcomes (PFS and OS) were proven within the trial. Since the cost of cetuximab is the key driver of the cost difference between the treatment arms, individual patient data were used in order to accurately calculate its cost.

The main weakness in the economic evaluation is the uncertainty involved in imputing values for the censored data. However, this weakness should not be over-stated, because sensitivity analyses show that the cost-effectiveness of cetuximab is robust to various methods of extrapolation and in fact the incremental cost-effectiveness ratio for cetuximab is below £20,000 per QALY even under the conservative situation of zero data imputation.

A second weakness is that utility data were not available directly from the pivotal clinical trial. Therefore it was necessary to estimate utilities based on a separate health state valuation study and a mapping exercise using individual patient data from the trial. Sensitivity analyses, however, reveal that the economic model results are not sensitive to the utility values used.

125. **What further analyses could be undertaken to enhance the robustness/completeness of the results?**

The pivotal clinical trial (Bonner *et al.*, 2006/EMR 62 202-006) included a quality of life instrument (EORTC QLQ-C30) from which it is unfortunately not yet possible to estimate utility values (refer to responses to questions 82 and 99), since a method is not available for mapping the EORTC QLQ-C30 to a utility instrument.

4. Assessment of factors relevant to the NHS and other parties

This section has been inserted because it was requested at an informal consultation meeting that an estimate of the budget impact be provided. The format of this section follows the May 2006 version of the STA guidelines. The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

4.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated budget impact for the NHS in England and Wales is £2.5m (treating 381 patients) in the first year of launch, rising to £6.7m (treating 1,015 patients) in the fifth year. Table 26 below presents total budget impact, purchase costs of cetuximab and associated other costs of administration.

Table 26 Budget Impact

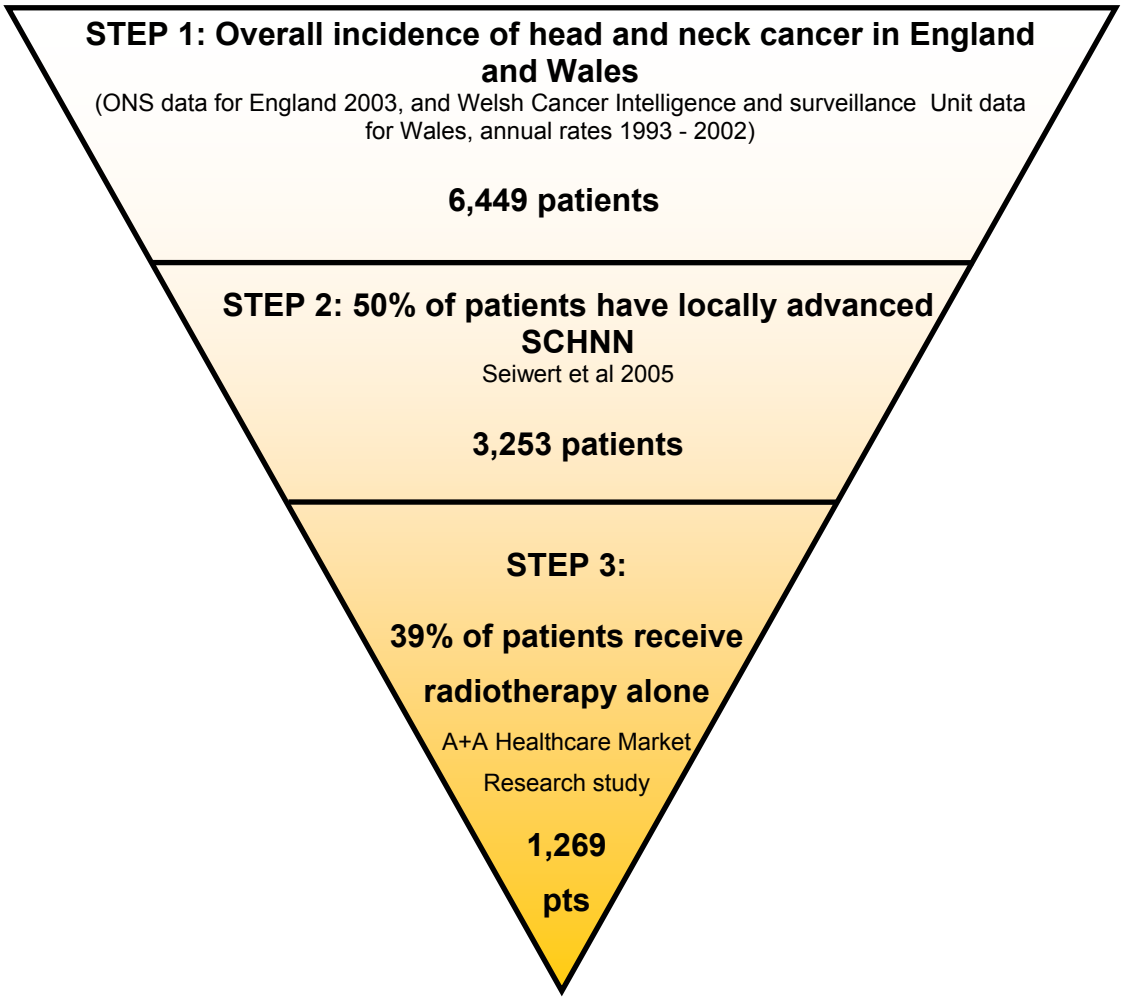
	2007	2008	2009	2010	2011
Cetuximab purchase costs	£ 2,091,351	£ 4,177,214	£ 4,874,331	£ 5,571,448	£ 5,571,448
Other costs of administration	£ 432,987	£ 864,838	£ 1,009,167	£ 1,153,496	£ 1,153,496
Total Budget Impact	**£ 2,524,339**	**£ 5,042,052**	**£ 5,883,498**	**£ 6,724,944**	**£ 6,724,944**

Approximately 80% of the budget increase is the purchase cost of cetuximab with the remaining 20% mainly being the administration and other costs associated. Other costs of administration include items such as therapy administration (15%), and monitoring (3.6%), with small cost additions from further adverse events, imaging, procedures and palliative care. Further details of incremental cost can be found in section 3.4.

4.2 What number of patients were assumed to be eligible? How was this figure derived?

Figure 9 below presents a schematic of the number of patients eligible for treatment in 2007.

Figure 9: Estimated number of patients eligible for treatment



Each step as presented in figure 9 will be described below.

STEP 1:

The overall incidence of head and neck cancer in England and Wales is estimated at 6,449 cases per year (2003) and taken from 2003 ONS data for and Welsh Cancer Intelligence and surveillance data for England and Wales respectively. Calculations of these epidemiology figures are presented below in table 27.

Table 27 Incidence estimates

Cancer Site	England *	Wales **	Total
C00-C14	4,295	n/a	n/a
C32	1,698	n/a	n/a
Total	5,993	456	**6,449**

* ONS data for England, 2003

** Welsh Cancer Intelligence & Surveillance Unit data for Wales, annual rates 1993-2002.

STEP 2:

This includes patients at all stages of disease, of which locally advanced disease is a subset. Table 28 below provides an overview of the TNM staging classification for SCHNN[14]. Locally advanced stages of SCHNN are shaded in the table in light grey. It is estimated, based upon estimates from Seiwert 2005 et al, that 50% of SCHHN patients have locally advanced disease.

Table 28 TNM Staging overview

Stage	T stage	N stage	M stage	Historic 5 year survival	Treatment goal	% of cases
0	Tis	N0	M0	NA	Curative	30-40%
I	T1	N0	M0	56-68.1%		
II	T2	N0	M0	45.4- 52.9%		
III	T3 T1-3	N0 N1	M0 M0	36.3 -56.3%	Curative	> 50%
IV A	T4a T1-4a	N0 or 1 N2	M0 M0	26.5- 38.9%		
IV B	T4b Any T	Any N N3	M0 M0			
IV C	Any T	Any N	M1	NA	Palliative	10%

Source: Adapted from an article by Seiwert et al (2005) who acknowledge the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, Inc.
5-Year survival, historically 1985 – 1991, rates vary depending on anatomic site of tumour
NA: not available/or applicable

STEP 3:

The estimated number of eligible patients for ERT treatment is 1,269 each year (i.e. 39% of locally advanced SCCHN patients). Please note that this is the estimated total number of locally advanced SCCHN patients who are currently treated with radiotherapy alone, and not all would receive cetuximb. For further information on estimated uptake rates of cetuximab please refer to section 4.4 for the estimated up-take rate. Table 29 below presents the estimated number of eligible patients over a five year period between 2007 and 2011.

Table 29 Estimated eligible patients

Year	2007	2008	2009	2010	2011
Number of patients	1,269	1,269	1,269	1,269	1,269

The eligible patient numbers were estimated from the annual incidence of head and neck cancer taking into account the proportion diagnosed in the locally advanced stage. The proportion who receive radiotherapy as opposed to chemoradiotherapy or surgery or palliative care also was considered, as described under Section 4.3. In the absence of any epidemiological source to suggest increasing incidence, and for the sake of simplicity it was assumed that the incidence of SCCHN was consistent over the five year period.

4.3 What assumption(s) were made about current treatment options and uptake of technologies?

The incidence figures cited above are sourced from registry data and as such they represent known cases, and it is assumed that all known cases received treatment (surgery, radiotherapy, chemoradiation, chemotherapy alone).

The National Clinical Audit Support Programme (NCASP) was contacted to determine whether the DAHNO (Data for Head and Neck Oncology) audit run by the NCASP could provide useful information for budget impact calculations. However, DAHNO is a relatively new audit collecting data prospectively, so

limited data are available at this time. Moreover, the available data are not collected at sufficiently detailed level to be useful for this submission.

The most useful data available for the budget impact model was market research. Two pieces of market research were considered; PiTRE Pharma[35] and the A+A Healthcare Market Research study referred to previously in section 3 of this submission.

The PiTRE Pharma study collected expert opinion from oncologists based on their treatment practice for all patients with locally advanced SCCHN regardless of whether they received any treatment for their disease i.e. clinical opinion on non-treated patients was also included. Face to face interviews were conducted with a structured questionnaire of 50 oncologists (40 clinical, 10 medical) in the UK in Dec 2004 – Jan 2005. Oncologists were asked to indicate, from their last 2 patient records, the proportion of patients given each treatment option, irrespective of surgery. The data indicated that the single most commonly used treatment strategy for locally advanced SCCHN is chemoradiotherapy (51%) although a substantial proportion of patients still received radiotherapy only (30%).

The A+A Healthcare Market Research conducted an audit of case notes from patients with SCHNN between October and November 2005 involving 52 hospitals from across the UK and collecting 405 patient case records. Patient case records were eligible for assessment if the patient was treated with either radiotherapy, chemotherapy or chemoradiotherapy. Table 30 below compares the two sets of results.

Table 30 UK treatment patterns

Treatment	Proportions (PiTRE)	Proportions (A+A)
Radiotherapy alone	30%	39%
Chemotherapy alone	8%	9%
Concomitant Chemoradiotherpay	51%	41%
Non concomitant Chemoradiotherpay	Not differentiated from Concomitant	10%
Palliative care	12%	Not collected

Sources: Market research, PiTRE (UKECRC05018); A+A Healthcare Market Research (UKEHN06001)

Based on the assumption that cetuximab will only be used in patients who would otherwise be treated with radiotherapy alone (irrespective of surgery), the number of patients eligible for treatment is estimated to be 39% of new cases of locally advanced SCHNN as supported by the A+A market research study. This data source was used since it collected actual patient level data, rather than opinion, and since it reflected the percentage of the actively treated population receiving radiotherapy alone, it ensured that total budget impact was not underestimated.

Thus it is estimated that of 6,449 new cases a year of SCHNN, 3,253 patients (50%) would be locally advanced and 1,269 (39%) of this group currently would be treated with radiotherapy alone (in the absence of ERT being launched). These patients would be eligible for ERT under the proposed intervention.

4.4 What assumption(s) were made about market share (where relevant)?

The pivotal clinical trial demonstrates that adding cetuximab to a radiotherapy regimen improves overall survival and locoregional control and does not significantly increase the risk of adverse events associated with RT. For patients who would be treated with radiotherapy alone, therefore, ERT offers an attractive treatment option. It is difficult to predict the uptake of ERT, so it

was decided to minimise the risk of under-estimating the budget impact of cetuximab by making a high prediction of the uptake rate in patients otherwise treated with radiotherapy alone. In addition it is worth noting that cetuximab is the first new class of therapy available for head and neck patients in 40 years, so we would expect a major survival benefit to be well received by the oncology community.

Thus, it is predicted that in the first year of launch, the uptake rate will be 30%, rising to 60% in the second year, 70% in the third year and 80% in the fourth and fifth years. Uptake rates and number of patients are presented below in Table 31.

Table 31 Uptake rates

Year	2007	2008	2009	2010	2011
SCHNN patients who would be treated with RT	**1,269**	**1,269**	**1,269**	**1,269**	**1,269**
Rate of Uptake	30%	60%	70%	80%	80%
Number of cetuximab patients	381	761	888	1015	1015

Thus the number of patients treated with ERT is estimated to be 381 in the first year, rising to 1,015 by the fifth year.

4.5 What unit costs were assumed? How were these calculated?

The results of the economic model (refer to section 3.4 (Q116)) were used to estimate the budget impact based on the estimated patient numbers. Unit costs were as used in the economic evaluation (refer to response to Q.85). Please find below a replication of Table 20 from section 3.4 (Q116) below presenting cost results.

Table 20 Cost results (replication of table 20 from section 3.4 (Q116))

Resource	RT	ERT	Increment
Study drug	£0	£5,489	**£5,489**
Radiotherapy	£2,661	£2,597	**-£63**
Therapy administration	£609	£1,621	**£1,012**
Adverse event costs	£760	£762	**£2**
Imaging	£293	£293	**£1**
Monitoring	£1,629	£1,868	**£239**
Procedures	£112	£112	**£0**
Palliative	£1,131	£1,078	**-£53**
Total	**£7,195**	**£13,821**	**£6,626**

Figures presented in the fourth column of incremental costs of ERT vs RT are those included within budget impact calculations. The total incremental cost of a patient treated with ERT vs RT is £6,626.

4.6 ***In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?***

As presented in section 4.3 above we have taken cost results as calculated for the economic model presented in section 3 of this report.

Budget impact figures are presented below in Table 32.

Table 32 Budget Impact

Year	2007	2008	2009	2010	2011
Number of cetuximab patients	381	761	888	1015	1015
Cetuximab purchase costs	£ 2,091,351	£ 4,177,214	£ 4,874,331	£ 5,571,448	£ 5,571,448
Other costs of administration	£ 432,987	£ 864,838	£ 1,009,167	£ 1,153,496	£ 1,153,496
Total Budget Impact	**£ 2,524,339**	**£ 5,042,052**	**£ 5,883,498**	**£ 6,724,944**	**£ 6,724,944**

4.7 Were there any estimates of resource savings? If so, what were they?

The economic model estimates that ERT is associated with a higher expected cost per patient than RT, with an incremental cost of approximately £6,626. The key driver of the cost difference is the cost of cetuximab acquisition, with all other cost categories being comparable between the two treatment groups.

4.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Whilst it is difficult to quantify, expert opinion has indicated that there may be savings to be made by avoiding the use and placement of PEG tubes which are required to overcome the long term side-effects incurred by radiotherapy and chemoradiotherapy, eg mucositis, dysphagia and xerostomia.

5 Appendices

Technical Appendix 1: Economic model variables

Appendix 1 - Economic Model Varia

Technical Appendix 2: Methods of statistical cure model

Appendix 2 - Cure Model.doc

Technical Appendix 3: Health state utility study

Appendix 3 - Utilities.doc

Erbitux SPC

Please see a copy of the SPC in the reference folder.

6 References

Please use the Vancouver style (i.e. consecutive numbering throughout the main text with up to six authors quoted in full followed by et al. in the reference list). There should not be any references in the summary. For example:

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