HEAD AND NECK CANCER TREATMENT: UTILITY VALUATION STUDY.

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- Economic Evaluation
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EXECUTIVE SUMMARY

The objective of this study was to estimate utility values for a series of health states describing major side effects and post-treatment outcomes that may be experienced by patients undergoing treatment (radiotherapy alone, cetuximab with radiotherapy) for locally advanced squamous cell carcinoma of the head and neck (SCCHN).

The intention is that these utility values will be used in an economic (cost-utility) analysis of cetuximab plus concomitant radiotherapy compared to radiotherapy alone for the treatment of locally advanced SCCHN.

Acute and late toxicities that differentiated between the three treatments were identified from randomised clinical trials data and/or supported by the opinion of a clinical expert. The differentiating side effects included mucositis, nausea and vomiting, acne type rash and haematological toxicities.

Seven health states described different grades of the acute toxicities, based on the National Cancer Institute (NCI) common toxicity criteria (CTC) for adverse events. Two further health states described late toxicities that may be experienced post-cessation of treatment. Two additional health states described possible final outcomes of treatment in terms of the success or failure of the treatment.

Nursing staff from oncology centres around the UK were recruited for the study (n = 50), and screened to ensure they had suitable experience in patient care and therapy techniques to be able to act as patient proxies. Each of the eleven health states were assessed by three methods;

- EQ-5D questionnaire
- EQ-5D visual analogue scale
- ranking

The mean utility values calculated from the EQ-5D along with mean VAS and ranks are shown in **Table 1**.

Table 1 Mean values (±1SD) for the three methods of assessing the eleven health states

Health state	Description	Mean scores (±SD)		
		EQ-5D quest.	EQ-5D VAS	Rank
A	Range of effects (Grade 0-1)	0.659(±0.131)	73.5(±17.14)	2.6(±1.57)
B	Mucositis (Grade 3 and 4)	0.062(±0.299)	23.5(±17.17)	8.8(±1.85)
C	Mucositis (Grade 2)	0.608(±0.310)	52.3(±16.55)	5(±1.52)
D	Nausea (Grade 3 and 4)	0.108(±0.350)	30.7(±16.72)	8(±1.71)
E	Nausea (Grade 2)	0.573(±0.247)	55.1(±17.37)	4.6(±1.56)
F	Acne/rash (Grade 3 and 4)	0.226(±0.404)	40.2(±20.11)	7.3(±1.7)
G	Haematological (Grade 4)	0.101(±0.392)	30.7(±19.17)	8.2(±1.96)
H	Peripheral neuropathy	0.473(±0.266)	57(±14.43)	4.9(±2.10)
I	Ototoxicity	0.657(±0.239)	60.9(±17.63)	4.2(±2.38)
J	Treatment success	0.862(±0.019)	82.6(±15.23)	1.8(±1.94)
K	Treatment failure	0.284(±0.040)	10.8(±11.81)	10.5(±1.13)

All three measurements predictably distinguish between grade 2 and grade 3 or 4 adverse events of the same category (e.g. B versus C and D versus E). The successful conclusion of treatment (J) was rated as the most desirable health state with the highest utility value. However, the scoring for unsuccessful treatment (K) differs between the measurement methods; in the case of both the VAS and rank data, K was judged the least desirable health state, but the EQ-5D questionnaire data attributes lower utility values to three other health states (D, G and B). This discrepancy between the measurements can be attributed to limitations in the EQ-5D that restrict assessment to five domains.

1 INTRODUCTION

This document reports the results of a UK utility valuation study of different health states representing adverse side effects arising from various treatments for locally advanced head and neck cancer. Health states representing possible post–treatment outcomes were also evaluated. The intention is that these utility values will be used in an economic cost–utility analysis of a new treatment for head and neck cancer.

1.1 DISEASE BACKGROUND

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 group of malignant tumours that affect areas such as the face, mouth, jaws, sinuses, throat, larynx, salivary glands, thyroid gland and neck. Greater than 90% of head and neck cancers (excluding the skin and thyroid gland) are squamous cell carcinomas, whilst 5% are melanomas, lymphomas, and sarcomas. There are over 30 specific sites (ICD10 codes) in this heterogeneous group of cancers and each particular one is relatively uncommon. However, the group as a whole is the sixth most common cancer worldwide and in England and Wales it accounts for over 8 000 cases and 2 700 deaths per year, excluding nasopharyngeal cancer.

1.2 DISEASE STAGES

Although simpler staging systems may be used in practice, head and neck cancers are traditionally classified clinically according to size and site of the primary neoplasm (T), number and size of metastases to the cervical lymph nodes (N), and evidence of distant metastases (M):

- Stage I: the primary neoplasm is less than 2 cm at greatest dimension or localised to one anatomic site without regional or distant metastasis (T1N0M0).
- Stage II: the primary neoplasm measures 2 to 4 cm at greatest dimension or affects two areas within a specific site (e.g. larynx) without regional or distant metastasis (T2N0M0).
- Stage III: the primary neoplasm is greater than 4 cm at greatest dimension or affects three adjacent areas in a specific head and neck site and/or has an isolated neck metastasis of less than 3 cm at greatest dimension (T3N0M0 or T1–3N1M0).
- Stage IV: the cancer is massive, invades bone and cartilage, and/or extends outside of its site of origin into another site (e.g. oral cavity into oropharynx). The neck metastasis measures greater than 3 cm; it affects multiple ipsilateral, contralateral, or bilateral lymph nodes or is fixed to surrounding tissue; and/or there is evidence of distant metastases (T1–4N1–3M0–1).

With appropriate treatment, the survival rate generally approaches 90% for stage I, 75% for stage II, 45 to 75% for stage III, and less than 35% for stage IV (Merck Manual online).

1.3 TREATMENT

The treatment of head and neck cancer is multi–disciplinary, combining medical imaging, surgery, radiation oncology, medical oncology, molecular oncology and histopathology. Early–stage head and neck cancer can be treated with curative intent employing surgery, radiation therapy (RT) or a multi–modality approach combining both radiation and surgery. In the case of stage III and IV head and neck cancer, patient outcomes can be improved by the addition of chemotherapy (CT) to RT, sometimes also referred to as chemoradiotherapy (CRT).

CRT strategies include three approaches:

1. pre–RT/induction / neo–adjuvant CT;
2. concurrent/concomitant CT; and
3. post–RT/adjuvant CT

The strongest evidence available is in support of the use of concomitant chemoradiation therapy (CCRT), with significant increases in overall survival compared to RT alone, having being shown in a number of recent individual studies (e.g. Adelstein *et al*. (2003) and several recent meta–analyses Pignon *et al*. (2000) updated in Bourhis *et al*. (2004) and Browman *et al.* (2001)). This has lead several clinical practice guidelines to conclude that CCRT with conventional fractionated radiotherapy should be the treatment of choice for patients with advanced SCCHN who are able to tolerate the toxicity (Head and Neck Cancer Disease Site group, 2000) (NCCN head and neck cancers panel members, 2005).The evidence in favour of induction chemotherapy and adjuvant chemotherapy, however, is not conclusive.

However, although there is increased therapeutic effect, toxicity–related adverse events are also increased when chemotherapy is added to radiotherapy. A recent study which compared conventional fractionated RT with an identical radiation therapy combined with cisplatin, found that grade III to V toxicities occurred in 52% of patients on RT alone and 89% of patients on CRT using cisplatin. Mucositis in particular has a major impact on patient quality of life, and the rates of mucositis/dysphagia were 33% for RT and 45% for CRT (Adelstein et al., 2003).

Thus, in light of the toxicity problems, a recently published practice guideline (NCCN head and neck cancers panel members, 2005) made the following recommendations for medics with patients newly diagnosed with unresectable loco–regional SCCHN:

- Performance status of 0–1: CCRT
- Performance status of 2: RT alone
- Performance status of 3: RT alone or best supportive care.

In the UK, expert advice (from Professor Chris Boshoff, Wolfson Institute for Biomedical Sciences, University College London) has indicated that the optimal treatment protocol for locally advanced non–resectable head and neck cancer is CCRT involving once–daily (five days per week) RT (total dosage of 60–74 Gy, over six to eight weeks, not including concomitant boost) and cisplatin (once per twenty one days, three cycles, at 100 mg/m^2 dosage). It should be noted that the optimal CRT would be that received by patients should they be fit enough to receive all three cycles of cisplatin. Such treatment is considered superior in terms of survival outcome than RT alone (Pignon et al., 2000); (Browman et al., 2001).

1.4 CETUXIMAB

Cetuximab (Erbitux™) is an IgG_1 monoclonal antibody that selectively blocks the epidermal growth factor receptor (EGFR). Epidermal growth factor has been implicated in the growth and progression of a range of cancers, including SCCHN. By blocking the EGFR, cetuximab reduces the strength of growth promoting signals that contribute towards the formation of the cancer.

Cetuximab with concomitant RT has been found to be more effective than RT alone in both loco–regional control and prolonging survival time in patients that have been diagnosed with locally advanced head and neck cancer. These benefits have been reported with little change in the adverse event profile compared to that expected from RT alone (Bonner, 2005). Based on the favourable comparison of adverse event profile with RT alone, it is anticipated that RT with concomitant cetuximab may be associated with fewer or less severe side effects than is seen with standard practice CCRT.

2 OBJECTIVE

The study objective is to obtain estimates of the health state utilities associated with adverse effects that can be substantiated to differ between RT alone, CRT using cisplatin (RT plus CDDP) and RT plus cetuximab.

The intention is that the utility estimates obtained in this study will be applied to an economic (cost–utility) analysis of cetuximab plus RT for the treatment of locally advanced head and neck cancer.

3 METHODS

3.1 INSTRUMENTS

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 head and neck cancer and post–treatment outcomes. These health states were assessed using the EQ–5D questionnaire.

The EQ–5D is a multi–attribute instrument that consists of two parts, a questionnaire and a visual analogue scale (VAS). The questionnaire is used to describe an individual's health status using five dimensions or domains, each of which has three levels. This generates two hundred and forty three possible health states, added to which are "unconscious" and "dead", making a total of two hundred and forty five health states that can be described by the EQ–5D (see **Appendix 1** for EQ–5D questionnaire used in the study).

Utility values are derived from the scores of the EQ–5D questionnaire by applying an algorithm linking the five digit health state descriptions with average utility tariffs derived from a survey of a representative sample of the UK general population using the time–trade off method (Dolan, 1997).

The VAS component of the EQ–5D requires the respondent to assess the health state and indicate its value on a scale ranging from 0 to 100.

The respondents were also asked to assess the health states by ranking them in order from best to worst. This assessment was included to act as a further measure of internal consistency.

3.2 RESPONDENT GROUP

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.

3.3 DEVELOPMENT OF THE HEALTH STATES

Most patients undergoing treatment for locally advanced head and neck cancer are likely to experience one or more adverse side effects from their treatment, the nature and severity of which will largely depend on the type of treatment they receive.

The intention here was to design a series of heath states to describe possible experiences of patients undergoing treatment for locally advanced head and neck cancer, according to the type and severity of adverse event being experienced.

To avoid cognitive overload for respondents taking part in the valuation, the number of health states included in the utility valuation were limited to those describing a combination of major adverse events and their severities that could be substantiated to distinguish between different comparator treatments to be included in the economic evaluation associated with this study. Furthermore, due to the limitations of the number of health states to be included in the study, the series of health states were designed to reflect increases in severity of only one adverse side effect at a time rather than increases in severity of combinations of side effects.

3.3.1 Identification of distinguishing treatment–related adverse events

Ideally, the best evidence to support the relative risks of adverse side effects is derived from data from adequately powered randomised trials that directly compare the comparator therapies. However, data from studies that have simultaneously compared cetuximab plus RT and CCRT using cisplatin are lacking. Consequently, identification of distinguishing adverse side effects and the associated risks of experiencing those adverse events while undergoing either of these treatment therapies has to involve a strategy of indirect comparison, via the RT arms of trials that have compared CCRT using cisplatin with RT and a single trial that has compared cetuximab plus RT with RT.

A literature search (using MEDLINE and EMBASE) was undertaken to identify randomised controlled trials comparing RT and CCRT, specifically using cisplatin, in patients undergoing

treatment for locally advanced head and neck cancer. A total of 16 trials were identified. A tabulated data–extraction (see **Appendix 2)** indicated a deal of inter–trial variability in terms of dosing/combination of CT and/or type/dosing of RT employed and patient population characteristics and in some cases this clearly impacted on adverse event outcomes. However, five trials (Cooper *et al*, 2004; Bernier *et al*, 2004; Fountzilas *et al*, 2004; Adelstein *et al* 2003 and Forastiere *et al* 2003) contained study arms where the cisplatin dosing and radiation schedules were similar to that considered optimal practice within the UK (see **section 1.3**). The intention was therefore to base the adverse events attribute levels as far as possible on these trials and bridge them with that of the trial of Bonner (2005) that compared RT with cetuximab plus RT, via the respective RT arms, specifically in the sub–group of patients in the trial that received standard (once daily) RT.

Treatment–related toxicities that distinguished between RT plus cisplatin and cetuximab plus RT treatments were identified, based on both the available trial data and the advice of a clinical expert (Professor Boshoff). The distinguishing toxicities and supporting information sources are summarised in **Appendix 3** and **Appendix 2** respectively, and listed here in **Table 2**.

Table 2 Distinguishing treatment–related adverse events

Adverse event
stomatitis/mucus membrane disorders
nausea/vomiting
Haematological toxicities
rash/acne
Late toxicity – peripheral neuropathy
Late toxicity – ototoxicity

One further AE not include in **Table 2** is allergic reaction following intravenous drug treatment. This risk is higher for treatments involving the administration of cetuximab than compared with RT or CCRT with cisplatin. However, this adverse effect was not included here as immediate treatment is available from the available clinician.

3.3.2 Health state descriptors

A series of eleven health states were devised. Seven of the eleven health states were designed to describe various experiences of patients on treatment according to the nature and severity of adverse events they were experiencing. These health states were framed in terms of the patient being midway through their treatment.

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) (see **Appendix 4** for the CTC definitions). 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

Two additional states described late toxicities (ototoxicity and peripheral neuropathy) that can occur post treatment. The two remaining health states described possible treatment outcomes in terms of success or failure of the treatment (i.e. loco–regional control and progressive disease) .

The eleven health states are summarised in **Table 3** and the set of complete health states descriptors is provided in **Appendix 5**.

Table 3 The eleven health states included in the utility study

Health state	Definition
A	General in–treatment– range of ≤ grade 1 adverse events
B	As health state A plus grade 3 or 4 mucositis, stomatitis and dysphagia
C	As health state A plus grade 2 mucositis, stomatitis and dysphagia
D	As health state A plus grade 3 or 4 nausea and vomiting
E	As health state A plus grade 2 nausea and vomiting
F	As health state A plus grade 3 or 4 acne and rash
G	As health state A plus grade 4 haematological toxicity
H	Post treatment –late toxicity: Peripheral neuropathy
I	Post–treatment –late toxicity: Ototoxicity
J	Post–treatment Loco–regional control (successful treatment)
K	Post–treatment Progressive or worsening disease (unsuccessful treatment)

3.3.3 Time frame of health states

When respondents were asked to give a utility score to each of the health states, they were asked to consider that each health state would be experienced for one month's duration. Health states A to I were assessed in the context of occurring during treatment, while J and K were post–treatment.

3.4 FIELD STUDY

The recruitment of respondents and interview field work for the study was conducted by our preferred partners, Silverfern Research International.

3.5 RECRUITMENT AND SAMPLE SIZE

A sample size of 50 was considered large enough to produce meaningful descriptive statistics. To ensure their suitability as patient proxies, particularly their background and familiarity with the patient experience during treatment, the oncology nurses were screened before being accepted onto the study (see **Appendix 6** for a copy of the screening questionnaire). The following criteria were required to be included in the study:

- A minimum of two years experience of working as a nurse in medical oncology.
- Eleven patients or over with SCCHN attending the clinic in the last three months.
- Experience in treating patients with RT, CT or CCRT.

3.5.1 Ethical considerations and remuneration

Informed consent was obtained from all participants. Contact and re–contact with respondents was made only via the interviewers. No names of respondents were collected or retained during the conduct of the survey (only initials) and therefore all respondent data were de–identified to M–TAG at the outset. Individual response data were treated as confidential both during and on completion of the study. Eligible participants who agreed to take part were paid an honorarium for their time.

3.5.2 Interview process

Once the initial screening assessment was complete, all interviews were carried out face to face with a trained interviewer who guided the respondents through the questionnaire. The questionnaire consisted of a brief introduction describing the exercise, and was followed by a practice question to familiarise the respondent with the EQ-5D instrument. In the practice question, the respondent had to assess their current health state by using the EQ-5D questionnaire and visual analogue scale.

The questionnaire then provides details of the scenario to be considered during the interview. Respondents were asked to consider the eleven health states describing different outcomes during and after therapy for SCCHN (see **Section 3.3.2**) in the context of a patient with the following profile: 50 to 70 year old male with a tumour located on tonsil, tongue or larynx. Assessment of these health states was first of all carried out using the EQ-5D questionnaire. Respondents were then given cards describing the health states and asked to arrange them in order of increasing severity and to record the rank on the sheet provided in the questionnaire. The final task of the interview involved recording an overall assessment of the health states using the VAS (see Appendix 1 for a copy of the complete questionnaire that includes details of all instructions received by respondents).

3.6 TREATMENT AND ANALYSIS OF DATA

information including answers to screening questions, demographic data and health state ratings for the EQ–5D questionnaire, VAS and ranks were entered into a Microsoft Excel spreadsheet database. As a quality control check for data entry, twenty percent of data inputs were checked for accuracy by a second researcher and amendments made where necessary.

Any respondent information or survey data that required clarification for any reason (e.g. missing data, poor hand writing, response ambiguities etc) were catalogued by respondent identifier code and communicated by M–TAG to Silverfern International and were then in turn passed on to the relevant interviewer. The interviewers were responsible for re–contacting the respondents in question and relevant pages of the questionnaire containing responses that required clarification were faxed to them. Clarifications, identified only by respondent code and initials, were then returned to M–TAG via Silverfern International.

In the case of one interviewer, sickness has prevented further clarification of missing demographic data. In this instance, descriptive statistics were calculated without the missing data. In all presentation of descriptive statistics, the sample size is given.

Descriptive statistics were calculated in Microsoft Excel (means, standard deviations, standard errors, medians, modes, maximum and minimum values, inter–quartile ranges and 95% confidence intervals) and checked by an experienced user.

4 RESULTS

4.1 QUALITY CONTROL OF DATA

Quality control analysis was carried out by an independent researcher on a sample of 20% of data input showed a total of 3 errors in 980 entries, giving an error rate of data entry of 0.3% which was deemed acceptable.

4.2 RESPONDENT DEMOGRAPHIC DATA

The oncology nurses were recruited from centres throughout the UK, and the postcode of the nurse's residence was used to identify the region where they worked. Nurses were recruited from a total of 15 regions as identified by the first part of the postcode: Leeds (n = 3), Newcastle (n = 9), Durham (n = 1), Hull (n = 2), Kirkcaldy (n = 1), Bournemouth (n = 3), Glasgow (n = 7) London (n = 10) Liverpool (n = 2) Chester (n = 1) Brighton (n = 3) Perth (n = 1), Oxford (n = 2), Birmingham (n = 3), Gloucester (n = 1). A postcode was not available for one respondent.

Table 4 A table showing summary demographic data for the oncology nurses taking part in this study

Demographic		**Proportion of respondents**	**Percentage of respondents**
How many patients attend oncology centre in last 3 months?	< 5	0	0
	5–10	0	0
	11–20	9/50	18
	21–30	13/50	26
	> 30	28/50	56
Which therapies given to the patient?	Surgery	39/47	
	surgery and post–op radiotherapy	46/46	100
	Radiotherapy	46/50	92
	Chemotherapy	48/49	98
	concomitant chemotherapy and radiotherapy	48/49	98
Sex	Male	0/50	0
	Female	50/50	100
Employment	Full time:	50/50	100
	part time:	0/50	0
highest educational qualification:	diploma/vocational certificate	17/50	34
	undergraduate degree	7/50	14
	postgraduate diploma	8/50	16
	masters degree	1/50	2
	doctorate degree	7/50	14
	postgraduate specialist vocational training/postgraduate specialist registration	10/50	20
mean number of years working (±SEM)	8.4 (±0.59), n = 43		
mean age (±SEM)	37.2 (±0.96), n = 43		

To be able to act as patient proxies for this study, oncology nurses were required to have a minimum level of experience in patient care and therapy techniques. Data concerning the numbers of patients attending the oncology clinic over a three month period for locally advanced SCCHN are shown in **Table 4**. A minimum of eleven patients attending the clinic over this period were required to be accepted onto the study. The data show that 28 (56%) of the respondents came from centres that had over thirty patients per three months, while 13 nurses (26%) came from centres that had between 21 and 30 patients, and 9 nurses (18%) came from centres that had between 11 and 20 patients per 3 month period.

Table 4 also shows the number of nurses with experience in the different therapies for SCCHN. To be accepted onto the study, nurses had to have experience in at least one of the therapies of interest (radiotherapy, chemotherapy and radiotherapy with concomitant chemotherapy). Due to incomplete filling of the questionnaire by respondents, replies to all questions were not possible to collect. This is indicated where appropriate by showing the number of nurses who had experience in the therapy and the total number of respondents to the question. There was no single therapy used by all the nurses, probably reflecting the extent to which therapies must be tailored to patient's needs. A total of 31 nurses had experience in all three techniques of interest. Further demographic data for the study respondents are also shown in **Table 4**. Again, due to circumstances beyond our control, data were not available for some questions, and the size of the sample is given alongside the data. All respondents were female and in full–time employment (n = 50). Respondents had a mean age (±SD) of 37.2 years (±6.32; n = 43) with a mean (±SD) of 8.4 (±3.87, n = 43) years experience in oncology. In terms of education, 17/50 of respondents held a diploma or vocational certificate, 7/50 had undergraduate degrees, 8/50 had an postgraduate diploma, 1/50 had a masters degree, 7/50 had a doctorate degree, with the same proportion also holding specialist post–graduate or vocational training (full demographic data are presented in **Appendix 7 along with questionnaire used to collect the demographics**).

4.3 EQ–5D QUESTIONNAIRE DATA

4.3.1 Assessment for normality

Utility scores for the 11 health states were collected from all 50 respondents using the EQ–5D questionnaire. To assess the suitability of the dataset for subsequent analysis using parametric statistics, a test for normality was performed (Sapiro–Wilks). The results of this test show that at the 0.05 level of significance, none of the health state assessments had data that were distributed normally (see **Appendix 8** for p–values from the Sapiro–Wilks test for normality).

4.3.2 Summary statistics

The EQ–5D questionnaire summary statistics for health states A to K are shown in **Table 5** (mean, standard deviation and *n*). These data show that the highest mean (±SD) utility value (0.862 ±0.132) was attributed to health state J "loco–regional control of disease," equating to a successful completion of therapy. The lowest mean utility value (0.062 ±0.299) was found for health state B (grade 3 or 4 mucositis, stomatitis or dysphagia). Further descriptive statistics on these datasets are available in **Appendix 8**, while a table showing the allocation of responses to each of the three EQ–5D levels for each of the five domains is shown in **Appendix 9**.

Table 5 Summary descriptive statistics for the EQ–5D questionnaire

Health state	Mean utility	SD	*n*
A	0.659	0.131	50
B	0.062	0.299	50
C	0.608	0.310	50
D	0.108	0.350	50
E	0.573	0.247	50
F	0.226	0.404	50
G	0.101	0.392	50
H	0.473	0.266	50
I	0.657	0.239	50
J	0.862	0.132	50
K	0.129	0.266	50

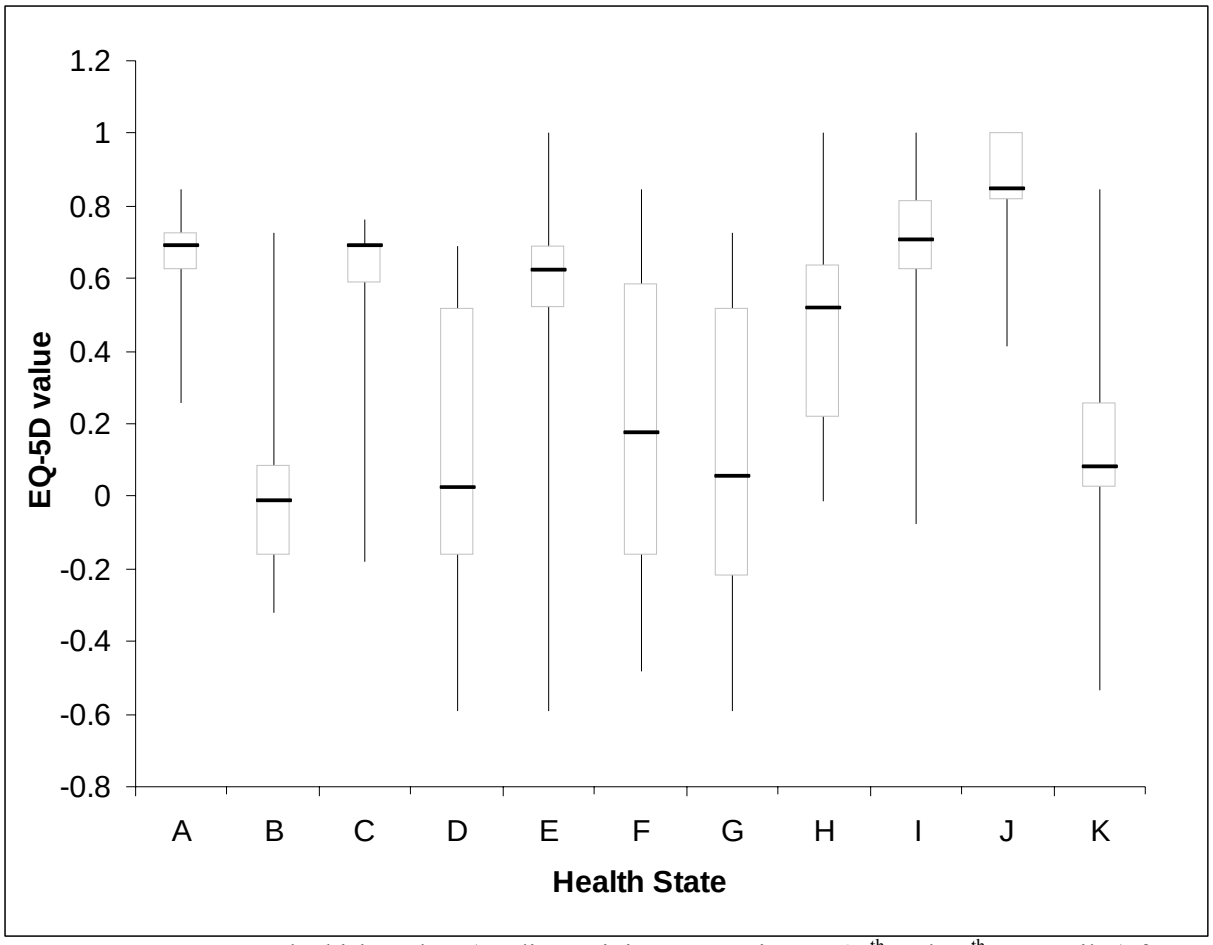

Figure 1 Box and whisker plots (median, minimum, maximum, 25th and 75th percentiles) for the EQ–5D questionnaire utility data

Box and whisker plots showing the median, minimum and maximum values, and 25th and 75th percentiles for the 11 health states assessed using the EQ–5D questionnaire are shown in **Figure 1**. These plots show how the median scores intuitively reflect some of the relative features of the health states. For example, the successful outcome of treatment (J) is scored highest, closely followed by general low grade 1 in–treatment effects (A). The utility values of the pairs of health states that vary only in the extent of the adverse effects differ predictably; mucositis at grade 2 (C) has a higher median value than mucositis grade 3 or 4 (B). Similarly, grade 2 nausea or vomiting (E) has a higher median value than grade 3 or 4 nausea or vomiting (D). One of the most surprising aspects of the EQ–5D questionnaire data is that treatment failure (K) does not have the lowest median value.

4.4 EQ–5D VISUAL ANALOG SCALE

It was not possible to collect all VAS data for all health states in the study. This was due to some respondents not assessing all health states presented in the questionnaire. In cases where no response was recorded, the summary statistics were calculated without missing data (*n* will therefore be less than 50).

4.4.1 Assessment for normality

Testing for a normal distribution using the Sapiro–Wilks test shows that, at the 0.05 levels of significance, health states A, F, I, J and K differ significantly from the normal distribution (indicated by a *p*–value of less than 0.05, see **Appendix 10** for *p*–values for the Sapiro–Wilks test for normality).

4.4.2 Summary statistics

The summary statistics (mean, SD and *n*) for the VAS evaluation of the health states are shown in **Table 6**, while box and whisker plots (median, minimum and maximum values, and 25th and 75th percentiles) are shown in **Figure 2** (for a full range of descriptive statistics see **Appendix 10**). These data show similar features to the EQ–5D questionnaire data: the successful outcome of treatment (J) is scored highest with a mean (± SD) of 82.6 ± 15.23, followed by the general in–treatment adverse effects (A) with a mean (± SD) of 73.5 ± 17.14. However, in contrast to the EQ–5D questionnaire data, the health state defining failed treatment (K) receives the lowest score with a mean (± SD) of 10.8 ± 11.81.

Again, similar to the EQ–5D questionnaire data, those health states that have the same adverse events but expressed to different extents differ predictably. The health states that represent mucositis at grade 3 or 4 (B) and 2 (C) have a higher score for C than B, and nausea or vomiting at grade 2 (E) has a greater median VAS than grade 3 or 4 (D). Those health states with grade 3 or 4 adverse events all score quite low; grade 3 or 4 mucositis (B) has a mean (±SD) of 23.5±17.17, nausea or vomiting (D) has a mean (±SD) of 30.7±16.72, acne or rash (F) has a mean (±SD) of 40.2±20.11, while late grade 4 haematological effects (G) has a mean (±SD) of 30.7±19.17.

Table 6 Summary descriptive statistics for the VAS scores of the eleven health states

Health state	Mean VAS rating	SD	*n*
A	73.5	17.14	50
B	23.5	17.17	50
C	52.3	16.55	49
D	30.7	16.72	50
E	55.1	17.37	50
F	40.2	20.11	50
G	30.7	19.17	49
H	57	14.43	49
I	60.9	17.63	49
J	82.6	15.23	50
K	10.8	11.81	49

No scores given by respondent 37 for health states C and K, by respondent 23 for health state G, by respondent 11 for health state I or respondent 50 for health state H

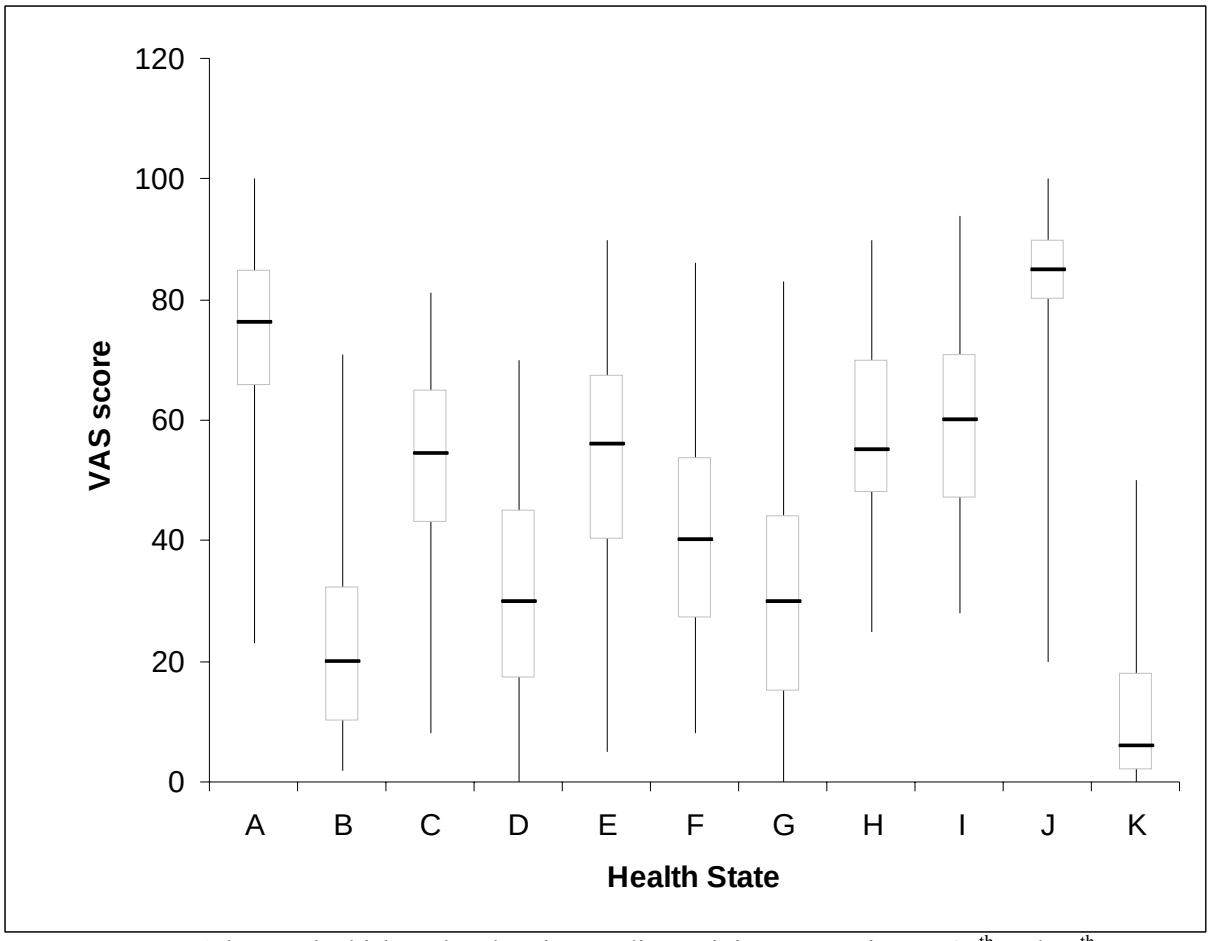

Figure 2 A box and whisker plot showing median, minimum, maximum, 25th and 75th percentiles for the VAS data

4.5 HEALTH STATE RANKS

The third dataset collected was based on the ranking of the 11 health states by the nurses, from rank one (best health state) to rank eleven (worst health state).

4.5.1 Test for normality

Analysis of these data using the Sapiro–Wilks test for normality shows that only data from three health states do not differ significantly from the normal distribution at the 0.05 level of significance: C, E and G. The rest of the health states form a distribution that is significantly different from normal (see **Appendix 11** for *p*–values from this analysis, *p*–values below 0.05 indicate a departure from normality).

4.5.2 Summary statistics

The highest ranking health state (relating to the healthiest of the 11 states) is health state J (loco–regional control) that had a mean (±SD) rank value of 1.8 (±1.94). The lowest ranking health state was K (progressive disease) with a mean rank (±SD) of 10.5 (±1.13) (see **Table 7**).

Table 7 Summary statistics of data from ranking assessment of health states

Health state	Mean Rank	SD	*n*
A	2.6	1.57	50
B	8.8	1.85	50
C	5	1.52	50
D	8	1.71	50
E	4.6	1.56	50
F	7.3	1.70	50
G	8.2	1.96	50
H	4.9	2.10	50
I	4.2	2.38	50
J	1.8	1.94	50
K	10.5	1.13	50

Some other characteristics of this dataset are presented in the form of a box and whisker plot showing the median, minimum and maximum values, and 25th and 75th percentiles in **Figure 3**. This plot shows several interesting features that are shared with the other datasets. Firstly, that a successful outcome of treatment (J) is ranked highest with a median rank of 1.8, while the unsuccessful treatment is ranked lowest with a median value of 10.5. Once again, there is a strong element of internal consistency in the respect that the pairs of health states that are either grade 2 or grade 3 or 4 of the same adverse effects are scored predictably, with the higher grade receiving a lower rank. For instance, C is ranked higher than B, and E is ranked higher than D.

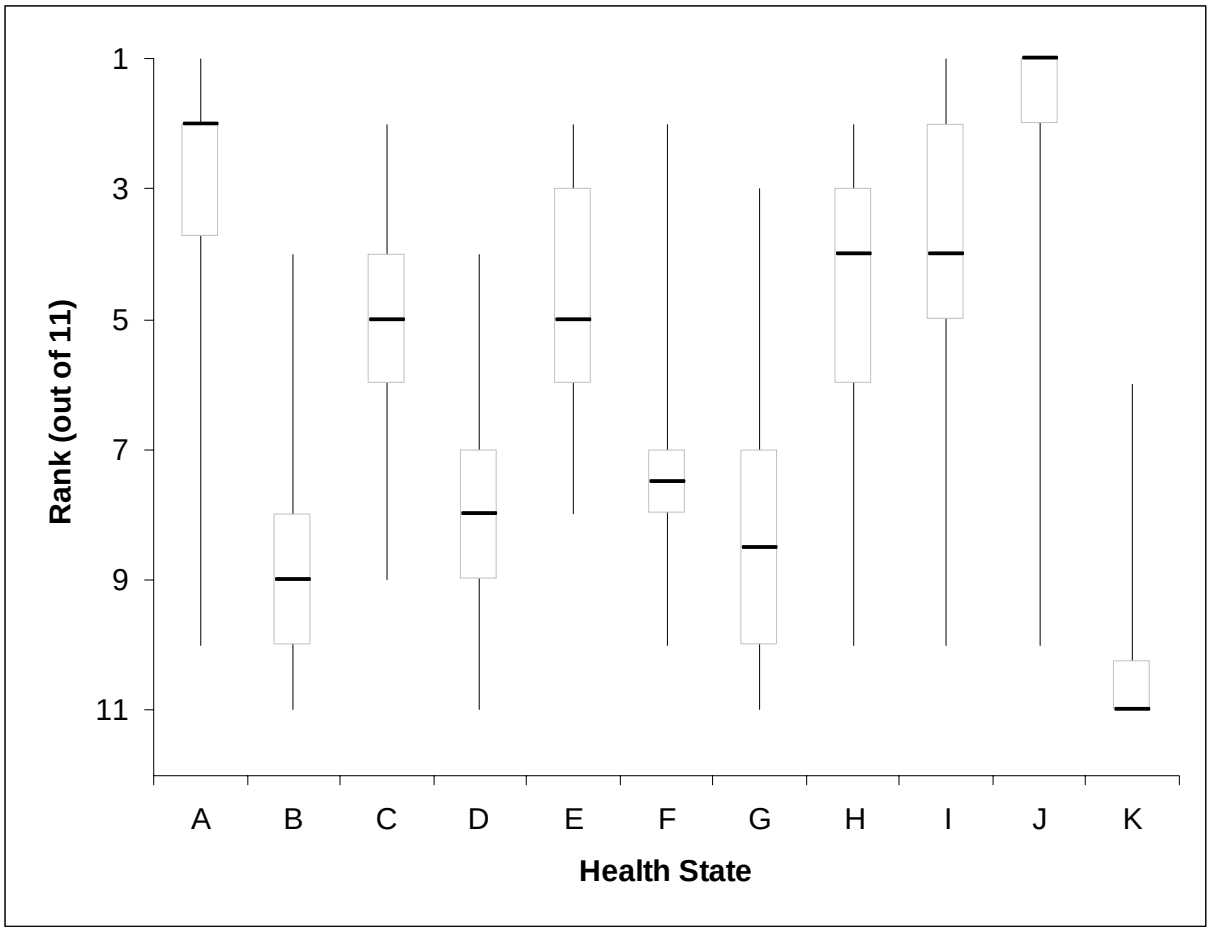

Figure 3 Box and whisker plots of the rank data showing median, minimum, maximum, 25th and 75th percentiles

4.6 COMPARISON OF DATA FROM EQ–5D, VAS AND RANKING

Comparison between the datasets is facilitated by placing them in order from best to worst health for the eleven health states. **Table 8** makes this rank comparison between the three measurements, and shows some regular features of the data. Health state J was consistently ranked as the highest, followed by A then I (the second and third highest scoring states respectively). The fourth, fifth and sixth positions vary between the different measurements, although all three have states C, E and H in these positions. Two of these health states, C and E, correspond to grade 2 severities for mucositis and nausea/vomiting respectively. The third health state (H) is a long term toxicity effect of peripheral neuropathy. These three states are scored similarly in all three measurements.

In a similar vein, health states that consistently ranked as the four worst are; unsuccessful treatment (K), grade 3 or 4 nausea (D), grade 3 or 4 mucositis (B) and haematological disorder (G). This group of health states share similar scores for each of the measurements, reflecting a similar grading of these acute, late toxicity and post–treatment effects. Within this group, one discrepancy that stands out is

that health state K was given the worse score using the VAS and ranking methods, however, in the case of the EQ–5D, there were three other health states that had lower average utility values.

Table 8 Comparison of the health state data (ranked best to worst) for the three measurements

EQ–5D (best to worst health state)	VAS (best to worst health state)	Rank (best to worst health state)
J	J	J
A	A	A
I	I	I
C	H	E
E	E	C/H
H	C	
F	F	F
K	D	D
D	G	G
G	B	B
B	K	K

5 DISCUSSION

Health states representing 11 possible outcomes resulting from either RT, CCRT or RT with concomitant treatment with cetuximab were assessed by nurses from specialist oncology centres around the UK. The nurses were chosen as patient proxies, and were screened before being accepted onto the study to ensure they had suitable experience of treatment methods and patient care on which to be able to base an assessment of the different health states. These data from the screening questions show that the nurses accepted onto the study had frequent experience with patients undergoing the treatments of interest for SCCHN, and therefore would have insight into the different health states experienced by the patients. In this respect, the nurses selected would be able to act as suitable patient proxies for this study.

Examination of te data show some variation between the results from the ranking and VAS assessments. As respondents were asked to rank the health states and then attribute VAS scores to each of them, it might be expected that the results from the health state rank and VAS score would show a strong correlation. This is not always the case however, and the results from approximately half of the respondents displayed some element of discrepancy between the measurements. The most likely explanation for this inconsistency is that respondents did not consider the health states in the order they ranked them when attributing the VAS scores. Instead, they may have worked through the health states in the order they were presented on the questionnaire, ultimately introducing an element of discrepancy between the two datasets.

Although the ranking exercise might be considered a warm up for the assignment of VAS values, the EQ-5D does not contain any such element. Therefore, a situation in which the influence of the ranking

on the VAS exercise is low bears a greater resemblance to the original EQ-5D instrument that has been validated for economic analysis.

However, when the means are considered, there was general agreement between the assessment methods concerning which health states were most desirable. All three assessment methods scored health state J (post treatment loco–regional control) as the most preferable, while A (grade 0 to 1 adverse effects from general in–treatment) was second, and I (ototoxicity) was third. This agreement in the assessment of the three highest scoring health states by three different methods of appraisal supports some degree of internal consistency between the evaluation techniques used.

Internal consistency can also be seen in the fact that the pairs of health states that consisted of the same adverse event occurring at different grades (grade 2 or grade 3 and 4) were scored predictably. For instance, the grade 3 or 4 nausea/vomiting (D) was consistently scored lower than grade 2 nausea/vomiting (E) using all three assessment methods. Similarly all measurements rated grade 3 or 4 mucositis (B) as worse than grade 2 (C).

The main instance where the scoring of health states varied between the different assessment methods was for health state K (treatment failure and disease progression). This health state was ranked as the lowest (mean rank of 10.5 out of 11) and had the lowest mean VAS score (10.8). However, the EQ–5D score did not reflect this assessment, and when ranked by mean EQ–5D score, health state K was ranked 8 out of 11 (see **Table 8**).

If the breakdown of how the scores of the different levels are distributed for each domain is examined for the EQ–5D questionnaire data (see **Appendix 9**) it is possible to see that while the anxiety/depression domain received the majority of its score for this health state from level 3 (extreme problem), the rest of the domains had the highest number of scores in level 2 (some problem). In contrast, health states such as B (grade 3 or 4 mucositis) had high number of level 3 scores for not only anxiety/depression, but also pain/discomfort. Ultimately, these differences between the relative assessments of health state K by the different measurement techniques, stem from limitations of the EQ–5D questionnaire in the different aspects of the health state that can be assessed. In the case of the VAS and ranking, the respondent is free to give a score or rank that reflects the total of all aspects of the health state, while the EQ–5D limits this assessment to just five domains.

Health state F (grade 3 or 4 acne/rash) was included in the study to represent a treatment–related side effect specifically associated with cetuximab. Although the cetuximab related rash may be unsightly and cause patients a level of anxiety and discomfort, it may be important to further explore whether

this health state descriptor, and thus whether the utility ratings obtained in this study, are a fair reflection of the level of disutility that might be associated with the cetuximab related rash. If the mean scores of each health state are ranked in order of utility, the rank of the cetuximab related rash is consistent between each of the measurement techniques; all methods showing it is ranked seventh.

Of the acute adverse effects, mucositis was consistently scored as being worse than the same grade nausea/vomiting, and also considered worse than same grade haematological effects in all three measurements.

6 CONCLUSION

Utility values have been derived for a number of hypothetical health states representing major adverse side effects that may be experienced by patients undergoing treatment for locally advanced head and neck cancer and possible post–treatment outcomes. The results of the study displayed a strong element of internal consistency in the rating, scoring and ranking of the different health states.

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APPENDIX 1: EQ–5D QUESTIONNAIRE USED BY RESPONDENTS

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APPENDIX 2: DATA EXTRACTION FROM THE FINAL LIST OF STUDIES

Adverse side effect		Comparator therapy	
		Concurrent CCRT (RT plus CDDP)	**Ctxmb plus RT**
When undergoing this type of cancer treatment, the percentage of people that can expect to experience this side effect is	Severe (Grade 3 or 4) Stomatitis/Mucous membrane disorders	39%[1] 43%[2] 68%[3]	23%[1] 22%[2] 52%[3]
	≥Grade 2 Nausea/Vomiting	18%+13% = 31%[4] 35%[5] 17%+17% = 34%[6]	1%+16% = 17%[4] 10–20%[5] 19%[7]
	Hospitalisation due toxicity as a result of cancer treatment	8.6%[8]	0.5%[9]
	Grade 3 or 4 Rash/Acne	1–2%[10]	16%[10]
	Allergic reaction following administration of intravenous drug therapy	< 1 %[11]	3–5%[11]
	Peripheral neuropathy	5%[12]	0%[12]
	Ototoxicity	5%[13]	< 1%[13]

CDDP, CDDP (100mg/m^2, days 1, 22 and 43); RT, RT (60–74 Gy over 6–8 weeks), 5 days per week);

[1]Based on pooled data from (Cooper et al., 2004), (Bernier et al., 2004); (Fountzilas et al., 2004), (Adelstein et al., 2003)and (Forastiere et al., 2003)for the occurrence of ≥grade 3 severity mucous membrane problems and/or stomatitis and an assumption of equivalence between RT and RT plus Ctxmb, based on data from Study 9815/006(50% versus 51.9%, respectively).

[2]Based on the occurrence of severe functional mucosal adverse events and mucosal necrosis for the RT and RT+CDDP arms in (Bernier et al., 2004)(22% versus 43%, respectively) and an assumption of equivalence between RT and RT+Ctxmb, based on incidence of mucositis in Study 9815/006(50% versus 51.9%). These data were considered by an expert advisor to be most representative of clinical experience. It should be noted that the higher percentages of mucositis in Study 9815/006a may be explained by the inclusion of twice daily (hyper–fractionated) and

concomitant boost RT regimens as well as standard once a day regimen, the former two regimens being generally associated with higher incidences of mucositis and stomatitis (Huguenin et al., 2004); (Brizel et al., 2004);(Jeremic et al., 2000) (Wendt et al., 1998); (Weissler et al., 1992).

[3]Based on the occurrence of ≥grade 3 severity mucous membrane problems reported for the Ctxmb plus RT arm in Study 9815/006 and the difference between the RT and RT plus CDDP in pooled data for occurrence of ≥grade 3 severity mucous membrane problems and/or stomatitis from (Cooper et al., 2004), (Bernier et al., 2004); (Fountzilas et al., 2004), (Adelstein et al., 2003)and (Forastiere et al., 2003). This is probably the least appropriate to represent risks associated with treatment practice in the UK as the Bonner study is derived from patients undergoing various modes of RT and not just from patients receiving standard once daily RT.

[4]Based on the pooled data from (Cooper et al., 2004), (Bernier et al., 2004); (Fountzilas et al., 2004), (Adelstein et al., 2003)and (Forastiere et al., 2003) for the occurrence (18% versus 1%) of ≥grade 3 severity nausea and vomiting with RT plus CDDP and RT alone, respectively, added to the frequency (12.7% versus 16.3%) of grade 2 severity nausea and vomiting reported for the RT versus RT plus Ctxmb arms of Study 9815/006l.

[5]Occurrences based on clinical experience of the expert advisor.

[6] Based on the occurrence (17.4%) of ≥ grade 2 severity nausea and vomiting reported for the RT plus arm of Study 9815/006 added to the difference (17%) between the pooled data from (Cooper et al., 2004), (Bernier et al., 2004); (Fountzilas et al., 2004), (Adelstein et al., 2003)and (Forastiere et al., 2003) for the occurrence (1% versus 18%) of ≥grade 3 severity nausea and vomiting with RT and RT plus CDDP, respectively.

[7] Based on the frequency (19.2%) of ≥ grade 2 severity nausea and vomiting reported for the RT plus Ctxmb arm of Study 9815/006.

[8,9] No trial data available for hospitalisations. Expert opinion has suggested that incidence of ≥ grade 4 haematolgical toxicities (anaemia, leucopenia, thrombocytopenia etc) may serve as a proxy for hospitalisation, although estimates may be conservative, particularly for the RT plus CDDP regimen, as ≥ grade 4 nausea and vomiting cases are also likely to require hospitalisation. [8]Based on the pooled data from (Cooper et al., 2004), (Fountzilas et al., 2004), and (Forastiere et al., 2003)(0.5% versus 8.6% for the RT versus RTplus CDDP arms) (Bernier *et al*, 2004 and Adelstein *et al* 2003 did not specifically report data for grade 4 toxicities).[9] Based on the assumption of equivalence between RT and RT plus Ctxmb supported by the incidences of ≥ grade 4 heamatological toxicities (0% versus 0%) reported for the RT versus RT plus Ctxmb arms in Study 9815/006l.

[10]Based on the data from Study 9815/006for acne type rash with an assumption that the acne rash is specifically due to Ctxmb, therefore equivalence assumed between RT and RT plus CDDP.

[11]Based on the clinical experience of expert advisor, supported by data of Study 9815/006 relating to the relative occurrence of hypersensitivity reactions (0% versus 2.9% in the RT and RT plus Ctxmb arms, respectively) and an assumption of equivalence between RT and RT plus CDDP

[12] Based on the pooled data from Cooper *et al*, 2004, Fountzilas *et al*, 2004, and Forastiere *et al* 2003 for the incidence (0% versus 4.5%) of ≥grade 3 neurological toxicities with RT and RT plus CDDP, respectively, with the assumption of equivalence between RT and Ctxmb plus RT, supported by expert opinion that suggested that the majority of neurological toxicities reported are likely to be peripheral neurotoxicities, that may be long lasting.

[13] No relevant data reported in Cooper *et al*, 2004, Bernier *et al*, 2004; Fountzilas *et al*, 2004, Adelstein *et al* 2003 and Forastiere *et al* 2003 therefore based on expert opinion, supported by the

Summary product Characteristics and PIL information supplied for Cisplatin (Electronic Medicines Compendium, eMC [Online])

APPENDIX 3: DESCRIPTION OF HEALTH STATES

	Health state title	Health state description
A	**General in–treatment** **Range of Grade 1 adverse events**	You are mid–way through your planned cancer treatment. You are experiencing side–effects that are not severe but make you feel poorly and may include one or more of the following: • You may feel like being sick and may have vomited once today • You may have mild pain or soreness in your mouth and throat • Swallowing may be a little painful • You are able to eat a normal solid diet
B	**Mucositis, stomatitis and dysphagia** **Grade 3 and 4**	You are mid–way through your planned cancer treatment. You are experiencing side–effects from the general in–treatment state that may include one or more of the following: • You may feel like being sick and may have vomited once today AND • You have Grade 3 or Grade 4 mucositis **or** stomatitis **or** dysphagia
C	**Mucositis, stomatitis and dysphagia** **Grade 2**	You are mid–way through your planned cancer treatment. You are experiencing side–effects from the general in–treatment state that may include one or more of the following: • You may feel like being sick and may have vomited once today AND You have Grade 2 mucositis **or** stomatitis **or** dysphagia
D	**Nausea and vomiting** **Grade 3 and 4**	You are mid–way through your planned cancer treatment. You are experiencing side–effects from the general in–treatment state that may include one or more of the following: • You have mild pain and soreness in your mouth and throat • Swallowing may be a little painful AND • You have Grade 3 or Grade 4 nausea **or** vomiting
E	**Nausea and vomiting**	You are mid–way through your planned cancer treatment. You are experiencing side–effects from the general in–treatment state that may include one or more of

	Health state title	Health state description
	Grade 2	the following: • You have mild pain and soreness in your mouth and throat • Swallowing may be a little painful AND • You have Grade 2 nausea **or** vomiting
F	**Acne and rash** **Grade 3 and 4**	You are mid–way through your planned cancer treatment. You are experiencing side–effects from the general in–treatment state that may include one or more of the following: • You may feel like being sick and may have vomited once today • You may have mild pain or soreness in your mouth and throat • Swallowing may be a little painful You are able to eat a normal solid diet AND • You have Grade 3 or Grade 4 acne **or** rash
G	**Haematological** **Grade 4**	You are mid–way through your planned cancer treatment. You are experiencing side–effects from the general in–treatment state that may include one or more of the following: • You may feel like being sick and may have vomited once today • You may have mild pain or soreness in your mouth and throat • Swallowing may be a little painful • You are able to eat a normal solid diet AND • You have a Grade 4 haematological disorder (leukocytopenia, neutropenia, granulocytopenia, anaemia, thrombocytopenia)
H	**Late toxicity: Peripheral neuropathy**	• You have completed your planned cancer treatment. • You are no longer experiencing any side–effects because of your cancer treatment • You feel as well as you did before you began your treatment except that you are experiencing some loss of feeling or numbness, tingling or pain in the upper and lower extremities of the body e.g. hands, feet, arms and legs,

	Health state title	Health state description
		which may interfere with carrying out your normal daily living.
I	**Late toxicity: Ototoxicity**	• You have completed your planned cancer treatment. • You are no longer experiencing any side–effects because of your cancer treatment • You feel as well as you did before you began your treatment except that you are experiencing hearing problems that may include some degree of hearing loss in one or both ears and/or tinnitus (ringing in the ears).
J	**Post–treatment Locoregional control** (Defined as no disease progression. Includes complete response, partial response and stable disease)	• You have completed your planned cancer treatment. • You are no longer experiencing side–effects due to the cancer treatment • Your response to treatment was positive, meaning that cancer progression has been halted. You may have experienced a complete response, a partial response or no change.
K	**Post–treatment Progressive or worsening disease** (Defined as an increase of at least 25% in tumour size for measurable tumours)	• Your cancer is progressing despite completing the first planned course of cancer treatment • Your signs and symptoms of disease have worsened • You may have received further treatment including surgery, radiotherapy or chemotherapy, or you may be receiving palliative care only

APPENDIX 4: COMMON TOXICITY CRITERIA

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APPENDIX 5: DEFINITIONS OF HEALTH STATES USED IN THE INTERVIEW

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APPENDIX 6: SCREENING QUESTIONNAIRE

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APPENDIX 7: RESPONDENT DEMOGRAPHICS

Demographics questionnaire used for the study:

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Table 9 The descriptive statistics for the respondent age and years worked in oncology

STATISTIC	AGE	YEARS WORKED IN ONCOLOGY
Mean	37.2	8.4
N	43	43
SD	6.32	3.87
SEM	0.96	0.59
Median	38.0	8.0
Mode	35	10
Min	24	2
Max	53	18
L 95% CI	35.34	7.23
U 95% CI	39.12	9.54

Table 10 The descriptive statistics for respondents marital status, employment basis and income

Demographic	Answer	Frequency
Marital status	Single	10
	Married/living with partner	32
	Widowed/separated/divorced	1
Employment basis	Full time	50
	Part time	0
Income	< £10, 000	0
	£10, 001 – £25, 000	20
	£25, 001 – £40, 000	20
	£40, 001 – £55, 000	9
	> £55, 001	1

APPENDIX 8: EQ–5D QUESTIONNAIRE DATA SUMMARY STATISTICS

Statistic	Health State										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
n	50	50	50	50	50	50	50	50	50	50	50
Mean	0.659	0.062	0.608	0.108	0.573	0.226	0.101	0.473	0.657	0.862	0.129
St Dev	0.131	0.299	0.310	0.350	0.247	0.404	0.392	0.266	0.239	0.132	0.284
SEM	0.019	0.042	0.044	0.050	0.035	0.057	0.055	0.038	0.034	0.019	0.040
Median	0.689	–0.012	0.689	0.024	0.620	0.174	0.053	0.516	0.707	0.848	0.082
Mode	0.689	–0.181	0.689	0.516	0.689	–0.181	0.516	0.516	0.689	1.000	0.082
Min	0.255	–0.319	–0.181	–0.594	–0.594	–0.484	–0.594	–0.016	–0.077	0.414	–0.536
Max	0.848	0.725	2	0.689	1	0.848	0.725	1.000	1.000	1.000	0.848
L 95% CI	0.622	0.021	0.522	0.011	0.504	0.114	–0.007	0.399	0.591	0.826	0.050
U 95% CI	0.695	0.145	0.694	0.205	0.641	0.338	0.210	0.547	0.723	0.899	0.208
IQ 25	0.62	–0.164	0.585	–0.163	0.516	–0.164	–0.221	0.2175	0.620	0.812	0.025
IQ 75	0.725	0.088	0.689	0.516	0.689	0.585	0.516	0.639	0.812	1	0.255
Sapiro–Wilks *p*–value	0	0	0	0	0	0.00025	0.021	0.00035	0.00001	0	0.032

APPENDIX 9: DISTRIBUTION OF LEVEL SCORES FROM EQ–5D

Health state being assessed	EQ–5D Level chosen	Domains of EQ–5D questionnaire				
		Domain – mobility	Domain – self care	Domain – usual activity	Domain – pain discomfort	Domain – anxiety/depression
A	1	37	42	14	5	4
	2	13	8	35	45	44
	3	0	0	1	0	2
B	1	22	18	3	0	0
	2	26	30	38	11	26
	3	2	2	9	39	24
C	1	34	35	10	0	3
	2	15	15	39	46	43
	3	1	0	1	4	4
D	1	9	4	1	0	0
	2	27	42	25	38	28
	3	14	4	24	12	22
E	1	30	31	10	1	4
	2	17	16	35	47	42
	3	2	2	4	1	3
F	1	27	14	6	1	2
	2	19	32	37	27	22
	3	3	3	6	21	25
G	1	10	11	1	0	0
	2	22	23	22	42	23
	3	17	15	26	7	26
H	1	7	10	6	13	3
	2	42	39	41	35	34
	3	0	0	2	1	12
I	1	32	47	17	22	3
	2	17	2	32	25	38
	3	0	0	0	2	8
J	1	46	48	41	41	18
	2	3	1	8	8	30
	3	0	0	0	0	1
K	1	16	14	5	3	0
	2	31	34	37	38	7
	3	3	2	8	9	43

APPENDIX 10: SUMMARY STATISTICS FOR VISUAL ANALOGUE SCORES

Statistic	Health State										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
n	50	50	49	50	50	50	49	49	49	50	49
Mean	73.5	23.5	52.3	30.7	55.1	40.2	30.7	57.0	60.9	82.6	10.8
St Dev	17.14	17.17	16.55	16.72	17.37	20.11	19.17	14.43	17.63	15.23	11.81
SEM	2.42	2.43	2.36	2.37	2.46	2.84	2.74	2.06	2.52	2.15	1.69
Median	76.3	20.0	54.5	30.0	56.0	40.0	30.0	55.0	60.0	85.0	6.0
Mode	85	20	65	45	50	40	10	60	70	80	0
Min	23	2	8	0	5	8	0	25	28	20	0
Max	100	71	81	70	90	86	83	90	94	100	50
L 95% CI	68.78	18.76	47.64	26.03	50.29	34.64	25.30	53.00	55.97	78.40	7.46
U 95% CI	78.28	28.28	56.91	35.31	59.91	45.78	36.03	61.08	65.84	86.84	14.07
Sapiro–Wilks *p*–value	0.000	0.208	0.518	0.457	0.266	0.075	0.531	0.213	0.000	0.000	0.000

APPENDIX 11: SUMMARY STATISTICS FOR RANK SCORES

Statistic	Health State										
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
n	50	50	50	50	50	50	50	50	50	50	50
Mean	2.6	8.8	5.0	8.0	4.6	7.3	8.2	4.9	4.2	1.8	10.5
St Dev	1.57	1.85	1.52	1.71	1.56	1.70	1.96	2.10	2.38	1.94	1.13
SEM	0.22	0.26	0.21	0.24	0.22	0.24	0.28	0.30	0.34	0.27	0.16
Median	2.0	9.0	5.0	8.0	5.0	7.5	8.5	4.0	4.0	1.0	11.0
Mode	2	9	6	7	5	8	10	3	2	1	11
Min	1.0	4.0	2.0	4.0	2.0	2.0	3.0	2.0	1.0	1.0	6.0
Max	10.0	11.0	9.0	11.0	8.0	10.0	11.0	10.0	10.0	10.0	11.0
L 95% CI	2.13	8.31	4.60	7.51	4.21	6.85	7.66	4.34	3.56	1.26	10.15
U 95% CI	2.99	9.33	5.44	8.45	5.07	7.79	8.74	5.50	4.88	2.34	10.77
Sapiro–Wilks *p*–value	0.000	0.001	0.790	0.012	0.398	0.004	0.066	0.012	0.008	0.000	0.000