EEPRU

Economic Evaluation of Health and Social Care Interventions Policy Research Unit

RESEARCH REPORT

Supporting the routine collection of patient reported outcome measures in the National Clinical Audits for assessing cost-effectiveness

Work Package 1

What patient reported outcome measures should be used in the 13 health conditions specified in the 2013/14 National Clinical Audit programme?

APPENDIX G, HEAD AND NECK CANCER

Authors: Roberta Ara, Ana Duarte, Sue Harnan, Jo Leaviss, Steve Palmer, Mark Sculpher, John Brazier

Correspondence to: Roberta Ara, HEDS, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA. Email: r.m.ara@sheffield.ac.uk

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The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 7 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care.

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Acronym	Definition
AE	Adverse events
BAHNO	British Association of Head and Neck Oncologists
DH	Department of Health
EORTC-QLQ	European organisation for research and treatment of cancer core quality of life questionnaire
FACT	Functional assessment of cancer therapy
EQ-5D	EuroQol 5 dimensions
FR	Future research
HRQoL	Health related quality of life
HS	Health states
HTA	Health technology assessment
MDT	Multi-disciplinary team
NCA	National Clinical Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PFS	Progression free survival
PR	Potential recommendations
PROM(s)	Patient reported outcome measure(s)
QALY	Quality adjusted life year
R&D	Research and development
RCT	Randomised controlled trial
STA	Single technology assessment
TA	Technology Appraisal
UK	United Kingdom
UW-QOL	University of Washington quality of life questionnaire
WP	Work package

1. **BACKGROUND**

EEPRU was approached by Jason Cox (R&D Division) to prepare a programme of research to support the appropriateness of, and use of, patient reported outcome measures (PROMs) collected for the National Clinical Audit (NCA). The EEPRU programme was informed by a Research aand Development (R&D) template prepared by Simon Bennett, Steve Fairman and Keith Willett at NHS England.

The purpose of introducing PROMs into the NCA programme is to be able to 1) compare performance between providers and commissioners in the National Health Service (NHS), 2) compare the cost-effectiveness of alternative providers in delivering the specific services (i.e. linking outcomes and resource use), and 3) assess the cost-effectiveness of alternative interventions and other changes in the NHS. The intention is to introduce PROMs across a range of conditions over the next 3 years commencing with 13 conditions in the 2014/15 NCA programme.

The agreed research programme consists of 3 concurrent work packages (WP) as described in the document submitted to the DH (8th November 2013). The current document provides details on the objectives, methodology and results for Work Package 1 (WP1): to determine what PROMS should be used in the 13 health conditions specified in the 2014/15 NCA programme.

2. **OVERVIEW**

WP1 is split into three separate components consisting of:

- WP1.1 To examine whether the Euro-QoL 5 dimensions (EQ-5D) is appropriate in the 13 health conditions specified in the 2013/14 NCA programme.
- WP1.2 To identify what measure could be used when the EQ-5D is not appropriate in the 13 health conditions, taking into account that the proposed measure would be used to generate preference-based utility measures (either directly through existing preference-based weights, or indirectly through existing mapping functions suitable for the proposed measure).
- WP1.3 To identify the evidence required to address questions of cost-effectiveness using the NCA data.

Each component consists of a series of reviews of the literature.

This Appendix provides the detailed results for the condition head and neck cancer and should be read in conjunction with both the main report and the methods/search strategy appendices.

3. METHOD

The full detailed methodology used is provided in Appendix A, including the search strategy, selection criteria for studies included, and data extraction etc. In summary, a review of the literature was undertaken to assess the appropriateness of the EQ-5D in terms of classic psychometric criteria (WP1.1); where the EQ-5D was not considered appropriate, additional searches were undertaken to identify alternative measures (WP1.2); and finally, existing health technology appriasials (HTA) were reviewed and data requirements were compared with variables currently collected in the head and neck cancer audit (WP1.3).

3.1 Psychometric properties (WP1.1)

Assessments reported in the included studies were categorised according to the following definitions:

Acceptability

Data relating to how acceptable the measure was to the person completing it, expressed as the proportion of completed surveys, or the proportion of missing data.

Reliability

There are two main definitions for reliability, a) the degree to which a measure reproduces the same results in an unchanged population and b) the degree to which a measure reproduces the same results when completed by different assessors (e.g. patient and proxy report). In both cases, reliability can be assessed by re-testing, and calculating the correlations or difference between tests. In case a) the comparison may be between the same populations separated by time, where no change in health state was observed (as compared to an alternative condition specific or generic measure). In case b) the measure may be completed by multiple people (proxies) on the patient's behalf and their responses compared with those of the patient. Where the outcome measure is specifically designed for self-report by patients, this test of reliability may be expected to produce less agreement.

Construct validity

This is an assessment of how well an instrument measures what it intends to measure. Two main definitions are used in this review.

a) Known group validity, where estimates for groups that are known to differ in a concept of interest are compared either qualitatively or statistically. The known groups may be defined using other measures, according to clinical categorisation.

b) Convergent validity assesses the extent to which a measure correlates with other measures of the same or similar concepts. Correlation coefficients were considered low if <0.3, moderate if between 0.3 and 0.5, and strong when >0.5.

Responsiveness

a) Change over time. This is an assessment of whether measurements using the instrument can detect a change over time, where a change is expected. This may be before and after an intervention, or through progression of a disease. Evidence was considered to be good where a t-test was significant, though weaker evidence to support responsiveness was considered where there was a change in the expected direction, but was not statistically significant or not tested. Effect size (ES) and standardised response mean (SRM) were also acceptable assessments of responsiveness.

b) Ceiling and floor effects were also considered to be indicators of responsiveness. Assessments of ceiling effects include the proportion of patients who score full health within a group of patients with known health detriments. A ceiling or floor effect can affect the sensitivity of the measure in detecting changes over time in patients at the extremes of the measure (for example those with severe disease activity and those with just minor symptoms of the condition).

3.2.1 **Alternative measures** (WP1.2)

Where evidence suggested the EQ-5D was not appropriate, or where no evidence was identified, alternative measures were reviewed.

3.3 **Evidence required for economic evaluations** (WP1.3)

The existing HTAs were reviewed alongside the variables currently collected in the NCA to determine if clinical or PROM data routinely collected in the NCAs would suffice to address questions of cost-effectiveness, and to identify any gaps in the evidence that would be required to compare providers, or the cost-effectiveness of interventions or policies.

4. RESULTS FOR HEAD AND NECK CANCER

4.1 Evidence of appropriateness of EQ-5D in head and neck cancer (WP1.1)

One review was identified through experts which covered all cancers.(1) No studies for head and neck cancer were found by this review. Searches were conducted in August 2010 in Longworth et al.(1) and an update was conducted by EEPRU in May 2014. The update searches retrieved 32 citations. None of these studies met the inclusion criteria of WP1.1. While two studies were identified in patients with brain cancer, this condition is excluded from the head and neck cancer NCA hence the studies are not reviewed here.

As such, there does not appear to be any evidence relating to the appropriateness of the EQ-5D in head and neck cancer.

4.2 Alternative measures in head and neck cancer (WP1.2)

Given the lack of evidence relating to the EQ-5D in patients with head and neck cancer, searches were conducted to identify what other generic or condition-specific measures could be used.

Seven documents were retrieved by the searches. Of these, only two related documents were relevant to WP1.2, both from the British Association of Head and Neck Oncologists (BAHNO).(2;3) Four of the remaining five were clinical guidelines and did not discuss PROMS,(4-7) and one was a report of a survey of patient experience, which did not include health related quality of life (HRQoL) outcomes.(8)

The two related documents from BAHNO comprise a multidisciplinary management guideline with a section on quality of life,(3) and a related document which discussed briefly quality of life questionnaire options, and described a recommended measure, the University of Washington quality of life questionnaire (UW-QOL v4).(2) There is, however, no mention of the measure in the management guideline, though a reference to it is given in the “further reading” section. Lowe & Rogers give no detail or background to their document, but it would appear that it is published by BAHNO, and can therefore assume endorsement.(2)

Lowe & Rogers state that there will be no perfect head and neck questionnaire, and cite a 2001 structured review of quality of life measures in head and neck cancer patients.(9) They also state “there is a choice between about 14 validated measures”, citing the same 2001 review and a 1999 review.(10) They cite EORTC (European Organisation for Research and Treatment of Cancer), FACT

(Functional Assessment of Cancer Therapy) and UW-QOL as the most commonly used measures, but prefer the UW-QOL v4 for its brevity and suitability for routine clinical practice.

Whilst the recommendation comes from a recognised professional body, there is no description of how the decision was reached, and no psychometric evaluation is in evidence. The document is also now somewhat out of date, having been published in 2008, and being largely based on a structured review conducted in 1999. Notably, a module specific to head and neck cancer (quality of life questionnaire head and neck 35 (QLQ-H&N35)) was developed to be used in conjunction with the EORTC QLQ-C30 at around the same time.(11) A brief search identified a systematic review of the psychometric properties of the QLQ-H&N35, published in 2013,(12) and which reported that construct validity and responsiveness had been rarely formally investigated, but that other psychometric properties were robust. They also reported that there was some room for improvement of the instrument in terms of methodological issues such as low internal consistency of some multi-item scales, and poor compliance of investigators in administering or reporting all scales within the tool.

Based on the limited evidence that was identified on alternative measures, in keeping with the recommendations for the bowel cancer audit, it is recommended that the EQ-5D and the EORTC QLQ-C30 (plus the QLQ-H&N35 module) are collected in the NCA with a view to assessing the psychometric properties of the measures using the NCA data (see Section 4.4).

4.3 **Evidence for economic evaluations in head and neck cancer** (WP1.3)

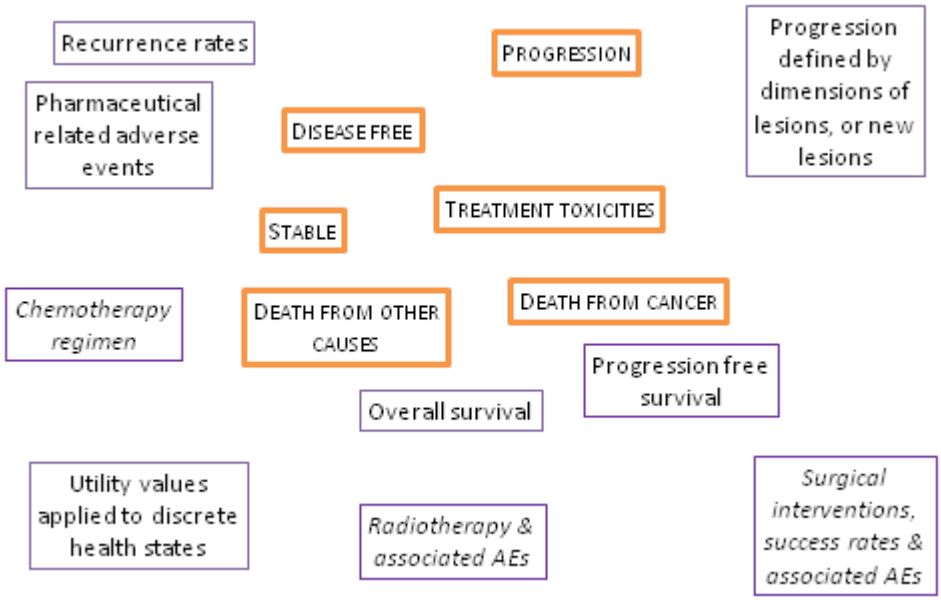
4.3.1 Cost-effectiveness modelling approach used in recent HTAs in head and neck cancer

Two single technology appraisals (STAs) relating to head and neck cancer were identified from the searches.(13;14) Both technology appraisals (TAs) examined the clinical and cost-effectiveness of a pharmaceutical intervention plus radiotherapy compared to radiotherapy alone in patients with recurrent and/or metastatic head and neck cancer,(14) or patients with locally advanced squamous cell carcinoma of the head and neck.(13)

State transition models were used to examine the cost-effectiveness of the interventions under appraisal. Both models consisted of discrete health states which represented the clinical pathway for people with head and neck cancer at the point of the intervention (Table 1). One STA restricted the number of health states to three (stable, progression, death) with progression defined as: a 25%

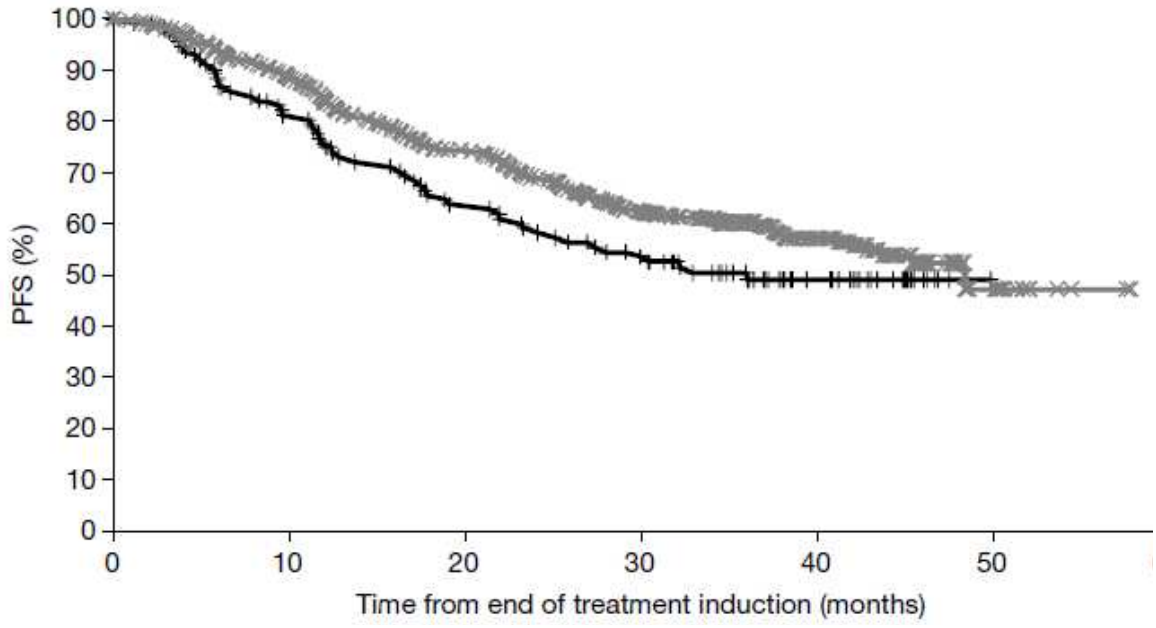
or more increase in the sum of the perpendicular dimensions of the index lesions compared to the smallest recorded in the study period, or the appearance of one or more new lesions, or uniquovocal progression of existing non-index lesions.(14) The second STA included additional health states for treatment toxicities (Table 1, Figure 1).(13) Progression and death were modelled using survival curves derived from RCTs (see Figure 2 for exemplar).

Figure 1: Modelling approach used in head and neck cancer HTAs



Legend: Orange framed boxes with uppercase text describe the health states used in the head and neck cancer TA models while the purple framed boxes with lower case (plain) text describe the evidence used. Italised text indicative of additional variables which would be informative for future economic evaluations in head and neck cancer.

Figure 2: Exemplar survival curves used to model interventions in cancer



PFS=Progression free survival

Both studies quality adjusted survival by assigning mean utility values to the discrete health states. Presumably due to the lack of more appropriate evidence, neither study used preference-based utility values obtained from patients with head and neck cancer. In the first study, proxy EQ-5D scores were obtained from a group of oncology nurses who were asked to judge how a patient with head and neck cancer would complete the EQ-5D questionnaire if they were experiencing particular sets of symptoms which included treatment toxicities such as grade 3 or 4 nausea and vomiting.(13) The second study used a published relationship to map from the European organisation for research and treatment of cancer core quality of life questionnaire (EORTC-QLQ) to the EQ-5D, using EORTC-QLQ data collected in the study used to describe the clinical effect of the intervention.(14) However, it must be noted that this was far from ideal as the data used to determine the relationship was obtained from patients with pancreatic cancer.

Table 1: Summary of existing models used in head and neck cancer TAs

Model approach	Method used to model utilities
STA (TA172): Head and neck cancer (squamous cell carcinoma) – cetuximab; 2009(14)	
State transition model 3 discrete health states: stable/response, progressive, death Effectiveness: survival curves Source: clinical studies	Utility: mapping EORTC QLQ-C30 to EQ-5D; mean values assigned to discrete HS Source: EORTC QLQ taken from RCT used for clinical effect (EXTREME trial); regression coefficients from people with pancreatic cancer -published literature AEs: assumed utility independent of treatment
STA (TA145): Head and neck cancer - cetuximab; 2006(13)	
State transition model 10 discrete health states: loco regional control, progressive disease, death, general in- treatment, general in-treatment plus: mucositis grades 3 & 4, mucositis grade 2, haematological grade 4, nausea and vomiting grades 3&4, nausea and vomiting grade 2, acne rash grades 3&4 Effectiveness: survival curves Source: clinical studies	Utility: proxy EQ-5D scores; mean values assigned to discrete HS Source: Oncology nursing staff (n=50) were given pre-defined health states relevant to head and neck cancer and asked to use their judgement on how a patient would complete the EQ-5D for each of these. Preference-based values then calculated using normal UK preference weights. AEs: described by the HS used

HS: health states; AE: Adverse Events; STA: Single Technology Appraisal; TA: Technology Appraisal; RCT: randomised controlled trial; EORTC QLQ: European organisation for research and treatment of cancer core quality of life questionnaire.

In summary, the following evidence would be required to compare providers or the cost-effectiveness of interventions for head and neck cancer:

- Condition severity
- Pharmaceutical interventions (type of intervention, concomitant medications, remission rates, relapse rates, adverse events)
- Progression measured using lesion(s) location and sizes
- Utility values
- Death with cause

The majority of this evidence would need to be linked through timings of collection.

4.3.2 Fields collected in the head and neck cancer NCA

The head and neck cancer audit collects data from hospitals in eligible trusts which diagnose and treat patients with cancer of the larynx and oral cavity (excludes tumours of the brain and thyroid cancers) in England and Wales. The fields in the head and neck cancer NCA are collected via an excel

spreadsheet completed by NHS staff. It is not clear which fields (if any) are mandatory (Appendix). The data collected relate to the first round of treatment during the clinical audit period, although additional multi-disciplinary team (MDT) records are included for each primary tumour. The fields provide information on patient characteristics (date of birth, name, postcode, gender, date of death); MDT discussion (clinical history, tests and results, tumour site, agreed care plan, recurrence indicator and date), surgery (provider, procedure code group and date, discharge date or death before discharge, pathological tumour site category, unscheduled return to surgery for same primary operation), non-surgical intervention (provider, date, type, radiotherapy, chemotherapy), palliative and nursing care, referral to speech and language therapists (SaLT), clinical status (primary tumour, nodes, metastasises), and nutrition.

4.3.3 Comparing fields in head and neck cancer NCA with variables used in existing HTAs

The existing models in head and neck cancer use survival curves for progression free survival and overall survival (OS). The information on clinical interventions (tumour, treatment, follow-up, Appendix) collected in the NCA would provide some of the information required to compare alternative treatments. The mortality data could be used to model overall mortality, and there may be sufficient detail to extract survival curves for progression and recurrence. It may also be possible to use the 'recurrence indicator' for relapse. Side-effects and adverse events due to chemotherapy, radiotherapy and surgery are prevalent. While there is some information on unscheduled return to surgery for the primary operation, there do not appear to be any fields relating to toxicity from chemotherapy or adverse effects of radiotherapy.

Patient related outcome measures are not currently collected in the head and neck cancer NCA. The inclusion of a preference-based HRQoL questionnaire such as the EQ-5D (alongside a condition specific measure such as the EORTC), would be useful for future economic evaluations, particularly as the existing HTAs do not in general use preference-based data to weight survival due to a dearth of evidence in patients with head and neck cancer. There are no variables collected in the audit which could be used to generate proxy HRQoL values through an established relationship due to the paucity of evidence on HRQoL in this population.

Assuming the fields have relatively high completion rates, with the exception of HRQoL, and toxicity/side effects of interventions, the information currently collected in the existing NCA may provide the majority of information required to model the cost-effectiveness of interventions and

policies in head and neck cancer. As previously noted, there is a dearth of preference-based HRQoL evidence in head and neck cancer, and the collection of a preference-based measure within the NCA would be recommended as an important and valuable consideration. It is understood that a feasibility study is scheduled sometime during the next couple of years, and it is possible that the new contract will include the collection of PROMs when the head and neck cancer NCA undergoes a retendering process later this year (2014).[personal communication, Eleanor Bunn, Audit Coordinator, 13th May 2014; personal communication, Julie, DAHNO Health And Social Care Information Centre, 10th July 2014]

4.4 Recommendations for head and neck cancer

The searches conducted to identify evidence on the appropriateness of the EQ-5D found no relevant studies. Although relatively old (2006 and 2009), the two TAs in head and neck cancer demonstrated that there were substantial gaps in the evidence base used to assign HRQoL scores along the clinical pathway for patients with head and neck cancer. The data used in these TAs do not satisfy the requirements of a submission to the NICE. The estimated, assumed, and predicted proxy utility scores increase the uncertainty in results generated from models. While it is likely that with exceptions, the current head and neck cancer audit collects much of the evidence needed to perform economic evaluations, this is far from clear. In addition, the head and neck audit is completed by clinicians/NHS staff and does not currently include a patient completed component. Potential recommendations (PR) and areas for future research (FR) are discussed below. All suggested future research areas are indicative and would require a discussion and detailed proposal if required.

It is clear that this is an area where research is required to inform the most appropriate PROM. The primary recommendation would be to consider collecting PROMs in this population, either through a postal questionnaire or electronically at strategic points in the care pathway (PR.1). It is recommended that the EQ-5D is considered for inclusion in the first instance to enable the evidence to be used to generate quality adjusted life years (QALYs) in economic evaluations. However, research would be required to determine the appropriateness of the EQ-5D in this population (FR.1), and it is recommended that a condition specific measure (such as the EORTC QLQ-C30 together with the QLQ-H&N35 module) is collected alongside the EQ-5D (PR.2).

Adverse events and side-effects of chemotherapy and surgical/radiotherapy interventions are prevalent and are key variables when assessing the benefits of interventions and procedures used in in cancer. It is recommended that these are included as mandatory variables in future audits (PR.3). It is also recommended that an appropriate measure of severity (such as mucositis grade) is collected alongside changes in lesions (PR.4).

Table 2: Recommendations and associated future research for head and neck cancer

PR.1	*Include a patient questionnaire or the provision for electronic collection of PROMs*
PR.2	*Include the EQ-5D in future patient questionnaires alongside a condition specific measure such as the EORTC QLQ-C30 and the QLQ-H&N35 module*
FR.1	*Assess the psychometric properties of the EQ-5D using the data collected in the head and neck cancer NCA*
PR.3	*Information on adverse events associated with chemotherapy regimens and the side effects of surgical interventions and radiotherapy*
PR.4	*Collect an appropriate measure of severity, such as mucositis grade alongside information on lesions*
PR.5	*Include additional mandatory fields in the head and neck cancer audit*
FR.2	*Detailed analyses of fields currently collected in the head and neck cancer audit to identify recommendations for future mandatory fields*

5. SUMMARY

5.1 Summary of evidence used to inform the conclusions for WP1.1 and WP1.2

One review was identified and an update search conducted. No primary research studies relating to the psychometric properties of the EQ-5D in head and neck cancer were identified. Searches identified seven published clinical or research guidelines relating to other measures, but none of these were based on up to date evidence. Given the limited evidence available, it is recommended that the EQ-5D is used alongside the EORTC QLQ-C30 and head and neck specific module, the QLQ-H&N35, in keeping with the recommendations for bowel cancer (Table 3).

Table 3: Summary of evidence currently available for recommended measure(s)

Condition	N	Acceptability	Reliability	Construct		Responsiveness		Overall
				KGV	Convergent	Change over time	Ceiling Effect	
EQ-5D	0	NE	NE	NE	NE	NE	NE	No evidence
Head and Neck Cancer	EORTC QLQ-C30 EORTC QLQ-H&N35	The psychometric properties of these measures have not been reviewed in the current report						

N= number of studies used to inform conclusions, KGV: known group validity; NE, no evidence was identified

5.2 Summary of evidence required for use in economic evaluations (WP1.3)

The head and neck cancer audit does not include a patient questionnaire thus PROMs are not currently collected and there does not appear to be an alternative field which could be used to predict the required preference-based utility values. Assuming there is a relatively high completion rate, it is thought that this audit collects much of the information required to derive survival curves for progression and recurrence of the disease but again key information may be missing such as condition severity (measured using information of lesions and required to case-mix when comparing providers), current pharmaceutical interventions (type of intervention, concomitant medications, remission rates, relapse rates, adverse events), surgical rates and complications.

APPENDIX: HEAD AND NECK CANCER

The tables in this Appendix provide additional information for the reviews (WP1.1, 1.2 and 1.3) conducted for head and neck cancer. There are no tables for WP1.1 as no evidence was identified.

Table A1: Mandatory fields collected in the head and neck cancer NCA

PATIENT
Date of birth, Postcode, Gender, Date of death
MDT DISCUSSION
Has patient had a pre treatment nutrition assessment, Year symptoms first noted, Chest XR performed prior to treatment, CT chest performed prior to treatment, , CT Primary / Neck performed prior to treatment, MRI primary performed prior to treatment, PET CT scan performed prior to treatment, Orthopantomogram (OPG) performed prior to treatment, Ultrasound performed prior to treatment, Biopsy procedure date, Date pathology report, Tumour laterality, Date of diagnosis, Primary site group, Primary site, Basis of diagnosis, Histological diagnosis at biopsy, First diagnosis organisation, Has HPV Status testing been done, HPV Test, HPV status, MDT organisation, Referral for cancer decision date, Has patient been discussed at MDT, MDT discussion date, Comorbidity index, Performance status, Care plan agreed date, Cancer care plan intent, Planned cancer treatment type 1, Planned cancer treatment type 2, Planned cancer treatment type 3, Planned cancer treatment type 4, Final Pre-treatment tumour site T Category, Final pre-treatment tumour site N Category, Final pre-treatment tumour site M Category, Has patient had a pre treatment nutrition assessment, Has patient had a pre treatment dental assessment, Recurrence indicator, Date of recurrence
SURGERY
Surgery provider organisation, Cancer treatment intent, Procedure date, Procedure code group 1, Procedure code 1, GMC 1, Procedure code group 2, Procedure code 2, GMC 2, Procedure code group 3, Procedure code 3, GMC 3, Procedure code group 1, Procedure code 4, GMC 4, Procedure code group 5, Procedure code 5, GMC 5, Procedure code group 6, Procedure code 6, GMC 6, "Did the patient die prior to discharge?", Discharge date, Date of post-resective pathology report, Post-resective histological diagnosis, Pathological tumour site T category, Pathological tumour site N category, Pathological tumour site M category, Was resective pathology discussed at MDT, Was there an unplanned return to theatre during the same admission for same primary operation?
NON SURGICAL
Treatment provider organisation, Treatment start date, Treatment type, Cancer treatment intent, Radiotherapy treatment to, Chemotherapy drug type
PALLIATIVE, NURSING AND SaLT
Palliative care organisation, Palliative care start date, Nursing care organisation, First CNS contact date, CNS present when patient advised of diagnosis, Has a patient concerns inventory been carried out? SaLT care organisation, First SaLT date, Was this patient assessed post treatment, Normalcy of diet (pre-treatment), Normalcy of diet at 3 months, Normalcy of diet at 12 months, Laryngectomy proposed method of post operative communication, Laryngectomy communication method (3 months post op), Laryngectomy communication method (12 months post op)
STATUS
Status recording organisation, Clinical status assessment date, Primary tumour status, Nodal status, Metastatic status
NUTRITION
Nutritional care organisation, Contact date (Dietician initial), Was the patient nutritionally assessed within 1 month of treatment, What was the predominant method of nutritional support during treatment, What was the predominant tube type used during treatment, Was patient seen within 6 weeks of completion of treatment?

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