Healthcare Improvement Scotland | SHTG Advice on health technologies

Evidence Note
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In response to an enquiry from Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde

What is the clinical and cost effectiveness of outpatient biopsy for diagnosis of suspicious lesions of the larynx, pharynx and tongue base?

What is an evidence note?

Evidence notes are rapid reviews of the evidence surrounding health technologies that are under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

This extended evidence note is based upon a review of the published clinical and cost effectiveness literature, and has been peer reviewed by experts across NHSScotland. It includes a budget impact analysis that has been carried out to assess the potential cost and resource impact of outpatient biopsy.

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Key points

- Studies were mainly retrospective and therefore at high risk of bias. None of the studies comparing outpatient biopsy with biopsy in an operating theatre used enhanced imaging.
- Outpatient biopsy was found to be safe with low complication rates. The majority of complications were self-limiting.
- The procedure appears to be well tolerated by most patients.
- Where there is clinical suspicion of malignancy, the high specificity of outpatient biopsy is sufficient to rule in diagnosis of malignancy. Low sensitivity of outpatient biopsy means that where there are negative findings patients will require a further biopsy under general anaesthetic in an operating theatre for confirmation.
- In NHS-relevant settings, there is evidence that the cost of the outpatient biopsy procedure is consistently lower than that of biopsy under general anaesthetic in an operating theatre.
- A budget impact analysis indicates that introducing outpatient biopsy is likely to be cost-saving over five years. Accounting for initial investment costs, the average resource saving per annum over five years is over £400,000.

1. Definitions

Definitions of terms relating to diagnostic test accuracy are provided in Appendix 1.

2. Literature search

A systematic search of the secondary literature was carried out between 14–22 February 2018 to identify systematic reviews, health technology assessments and other evidence based reports. Databases used were: Medline, Medline in process, Embase, Cinahl and Web of Science.

Medline was systematically searched between 14–22 February 2018 for primary diagnostic studies. Results were limited to primary diagnostic studies in English from 2008 onwards.

Key websites were searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: Flexible laryngoscopy, office-based, in-office, out-patient, operating room biopsy, direct laryngoscopy/microlaryngoscopy, narrow band, image guided. A full list of resources searched and terms used are available on request.

3. Introduction

Patients referred to ear, nose and throat (ENT) or head and neck outpatient clinics commonly undergo transnasal laryngoscopy to visualise the larynx, pharynx and tongue base. Where suspected malignant lesions are identified, the 'gold standard' investigation is direct laryngoscopy (also described as direct microlaryngoscopy or panendoscopy) with biopsy. This biopsy procedure involves the patient having a general anaesthetic in an operating theatre and, as well as anaesthetic risk, this carries risk of dental damage, and in some cases, requirement for tracheostomy. The need to schedule theatre time, an overnight or day-case hospital bed and pre-procedure assessment means that there can be a delay in commencing treatment.

The development of laryngoscopes that incorporate an instrument channel, and associated developments around visual enhancement/colour filtering image processers, means that, for some patients, outpatient biopsy can be conducted with local anaesthetic at the time of initial investigation[1, 2]. In this case, biopsy is performed using small (around 2 mm) forceps and sampling is guided by images enhanced to identify the highest risk tissue. Outpatient biopsy may expedite diagnosis and allow selected patients to avoid undergoing a general anaesthetic. There may also be economic benefits[3].

This evidence note examines the clinical and cost effectiveness of outpatient biopsy, with enhanced imaging (such as narrow band imaging, iScan or Spectra A/ Spectra B) for

diagnosis of suspicious lesions of the larynx, pharynx and tongue base. The comparator is biopsy under general anaesthetic in an operating theatre (operating theatre biopsy; OTB). This evidence note aims to assess whether adopting this technology might allow selected patients to avoid OTB, which involves general anaesthetic and longer hospital stay. The patient groups of interest comprise those who are high risk with respect to general anaesthetic due to co-morbid conditions, and those for whom surgical treatment is unlikely to be indicated.

4. Health technology description

The technology consists of a flexible laryngoscope with an instrument channel which is connected to an image processing platform. Biopsy forceps, which are available in a range of designs and mechanisms, are used to obtain tissue samples.

Examples of the systems include:

Olympus	ENF Type VT2	EVIS Exera II	Narrow band imaging (NBI)
PENTAX	FNL-15RP3	EPK-3000 DEFINA	iScan
Karl Storz	11101VP/VPS	Image 1S	Spectra A / Spectra B

5. Epidemiology

Oropharyngeal cancer incidence has increased in the last decade due to the rising prevalence of HPV infection[4].

In 2015 there were 348 new diagnoses of oropharyngeal cancer (encompassing tongue base) in Scotland (252 males, 96 females), which represents a European age standardised rate of 6.6 new oropharyngeal cancer diagnoses per 100,000 person-years at risk (95% confidence interval (CI) 5.9 to 7.3). In the same year, 103 deaths from oropharyngeal cancer were recorded in Scotland[5].

In 2015 there were 293 new cases of laryngeal cancer in Scotland (236 males, 57 females). This represents a European age standardised rate of 5.9 new diagnoses per 100,000 person-years at risk (95% CI 5.3 to 6.6). In the same year, 127 deaths from laryngeal cancer were recorded in Scotland[5].

In NHS Greater Glasgow and Clyde Board area, over 700 patients referred into ENT have examinations under anaesthetic each year. Based on a departmental audit 20-30% of patients presenting with head and neck cancer are treated palliatively (J Montgomery, ENT Consultant, Personal communication, 1 November, 2017).

6. Clinical effectiveness

No randomised controlled trials were identified comparing clinical outcomes, such as cancer survival or recurrence rates, between patients receiving outpatient biopsy and those undergoing OTB.

Diagnostic accuracy

It is notable that none of the diagnostic accuracy studies comparing outpatient biopsy with OTB incorporated enhanced imaging / NBI-guided outpatient biopsy. Blinded and unblinded prospective studies are outlined first before retrospective studies are described. In these studies typically over 80% of study participants were males and average age of patients was between 60 to 70 years.

Prospective observational studies

Two prospective observational studies examined the diagnostic accuracy of outpatient biopsy compared with OTB[6, 7].

The first study, conducted in a Spanish centre between 2008 and 2011, recruited patients over 18 years of age (n=76) with suspected malignant pharyngolaryngeal tumours[7]. All patients underwent outpatient biopsy and subsequent OTB. The OTB was conducted blind to the findings of the outpatient biopsy.

The sensitivity of the outpatient biopsy for diagnosis of malignancy was 81.1% (95% confidence interval (CI) 72.2% to 90%). All of the patients in the group had malignancy. This patient group was likely too small to reflect practice and ascribe validity to the reported 100% specificity. In discussing the findings, the study authors describe how sensitivity may be limited due to the ability to sample only a small portion of any lesion.

In the second prospective study, conducted in Israel from 2006 to 2009, 117 patients with suspicious-appearing lesions of the larynx were recruited[6]. For seven patients who were intolerant to the procedure, outpatient biopsy did not provide adequate tissue for pathological studies. These patients' data were excluded from the analysis. The outcomes for the remaining 110 patients were:

- 51/110 benign pathology, referred for OTB (OTB findings: 29 benign pathology, 18 invasive carcinoma, four carcinoma *in situ*)
- 17/110 carcinoma *in situ*, referred for OTB (five declined and excluded from analysis, OTB findings; 10 invasive carcinoma, one carcinoma *in situ*, one benign pathology)
- 42/110 invasive carcinoma, referred for staging and definitive treatment (no OTB conducted, all assumed to be true positives)

Based on 105 patients, the sensitivity for diagnosis of malignant laryngeal lesions was 70.6% and specificity was 96.7%.

Authors of these prospective studies suggest that the high specificity indicates ability of outpatient biopsy to rule in malignancy whilst the low sensitivity of the procedure means that all patients with clinically suspicious lesions where the outpatient biopsy suggests a benign pathology or carcinoma *in situ* should have verification by OTB.

Retrospective observational studies

Four retrospective studies were identified which reported measures sensitivity and specificity.[8-11]. Such studies are generally at high risk for selection bias. In the largest study, conducted in South Korea between 2011–2014, outpatient biopsy was performed in 581 consecutive patients with suspicious laryngeal lesions[8]. Not all patients had both outpatient biopsy and OTB. For over half of the patients negative for malignancy on initial outpatient biopsy (n=223), the true negative rate was determined by close follow up for six months. Sensitivity for malignancy was 78.2%, specificity was 100%.

In a study from the USA conducted between 2010–2013, a subset of 76 patients from a group of 261 having outpatient biopsy for laryngeal and pharyngeal lesions had OTB[9]. Patients with definitive diagnosis of malignancy on initial outpatient biopsy were excluded from the study. Sensitivity of outpatient biopsy for malignant or premalignant lesions in this series was 60% with specificity 87%.

In a study from Israel, conducted between 2013–2017, 238 patients had outpatient biopsy for suspicious laryngeal lesions[10]. Of these, 85 had a malignant result which was considered diagnostic and final, and 111 went on to have OTB. Based on all 196 patients, sensitivity of outpatient biopsy was 77.8% and specificity was 95.1%. Authors of this study suggest that for the three false positive results on outpatient biopsy it is likely that in two cases the tumour was excised with adequate margins during the initial biopsy. For the third, a squamous cell carcinoma was diagnosed on OTB three months later.

In a Spanish study, conducted between 2006 and 2016, 30 patients who had pharyngolaryngeal lesions suspected of malignancy were offered diagnostic confirmation by outpatient biopsy[11]. For one patient it was not possible to obtain an appropriate tissue sample due to intolerance of the procedure. For the remaining patients, 19 were diagnosed with malignancy and were referred for treatment, 10 patients had OTB with seven carcinomas identified. The sensitivity of the procedure compared with OTB was 73% and specificity was 100%.

Outpatient biopsy guided by enhanced imaging

Although none of the diagnostic accuracy studies comparing outpatient biopsy with OTB incorporated enhanced imaging guided outpatient biopsy, some relevant studies were identified. One prospective feasibility study from Finland - conducted during 2013 - examined the use of NBI in the examination of upper airway lesions (including oral) in an outpatient setting[6]. The comparison for this study was between white light endoscopy and NBI with the reference standard of biopsy. However, it was unclear from the study report if biopsy was conducted as OTB. The study concluded that outpatient biopsy was feasible in everyday practice. A retrospective study from a Taiwan[12] (n= 90) reported that NBI was associated with accurate sampling of outpatient biopsy for upper airway malignancy. Another study from this Taiwanese centre described the feasibility of this intervention in 19 patients with suspicious lesions who had difficult airways resulting from treatment of previous head and neck cancer[13].

Time to diagnosis/time to treatment

One retrospective study from Israel examined the effect of outpatient biopsy on time to diagnosis for 113 patients with suspicious lesions for whom full diagnostic information was available[10]. Those patients with malignant pathology on outpatient biopsy (n=53) received their diagnosis within a mean of 10.7 days, said to reflect the availably of the procedure being within one week, plus the 2-6 day turn-around period for the pathology report. The availability of OTB had approximately a one month waiting time. Those patients identified with benign pathology on outpatient biopsy who subsequently had malignancy identified (n=10) received their diagnosis in a mean of 49.1 days. No data were provided on time to diagnosis for patients referred directly for OTB.

Another retrospective study examined data on outpatient biopsy for 116 patients (92 transnasal, 24 transoral) and reported that mean time to treatment (surgery, radiation or chemoradiation) for patients with successful outpatient biopsy (n=97) was 24.2 +/- 13.9 days, whilst for those without it was 48.8 +/- 49.4 days (sic). A successful procedure was defined as one where a tissue specimen adequate for pathological diagnosis was obtained during outpatient biopsy[14].

7. Patient social aspects

Tolerability of the outpatient biopsy procedure

There was no consistent measure for patient tolerability within the evidence identified which makes it difficult to reach meaningful conclusions. One prospective study (n=88) did not encounter any problems with patient tolerance[7], whilst another reported intolerance to the procedure in one patient out of 30[11]. In retrospective studies, tolerability was often not discussed. It was likely that physician judgement as to patient suitability for the procedure

had been applied during patient selection. Factors which might exclude patients were outlined in one study as being unable to sit for prolonged time, a strong gag reflex, having respiratory distress or poor cardiopulmonary function[12]. One study of the safety of the technique cited excessive coughing or pharyngeal reflex as reasons for the procedure not being tolerated in two out of 201 procedures [15]. Two studies linked tolerability to rates of adequate sampling [6, 8] and reported achieving sufficient tissue for pathological examination in 94% and 99.1% of cases respectively.

Time to diagnosis/time to treatment are also factors likely to have an impact on patients' wellbeing.

8. Safety

No studies were identified comparing the safety of outpatient biopsy with OTB. Retrospective studies of outpatient biopsy with data relating to fewer than 100 participants were excluded.[9, 12-14, 16, 17] Information on complications from two prospective and three retrospective studies are shown in Table 1. Across studies, the proportion of patients experiencing complications was low and ranged from 0 to 2.6%. Complications were self-limiting in many cases. Studies differed as to whether the procedure required patients to desist from anticoagulant use with one study highlighting this as a drawback of outpatient biopsy[7] whilst another stated that anticoagulant use was not a contra-indication[15].

Table 1: Complications of outpatient biopsy

Study	Prospective/ retrospective	Number of patients	Complications
Cohen (2014)[6]	Prospective	117	Post procedure aspiration– no serious consequences (1 patient) Epistaxis, self-limiting (2 patients)
Castillo Farias (2015)[7]	Prospective	88	No airway or other critical concerns in any of the cases
Cha (2016)[8]	Retrospective	581	None
Cohen (2018)[10]	Retrospective	355 (390 procedures)	Epistaxis, self-limiting (2 patients) Haematoma (1 patient) Aspiration event – resolved spontaneously (1 patient)

Study	Prospective/ retrospective	Number of patients	Complications
Wellenstein (2017)[15]	Retrospective	187 (201 procedures)	Laryngospasm – self-limiting (1 patient) Anterior epistaxis – required intervention (1 patient) Laryngeal bleeding – required intervention (1 patient) Supraglottic oedema resulting in tracheostomy (1 patient)

9. Cost effectiveness

Five studies[7, 11, 16, 18, 19] reported costs of the procedures as study outcomes (or mentioned the costs in the discussion sections of the paper), but only two had conducted formal cost comparisons, and neither (one US-based and one Taiwan-based) were readily transferrable to a Scottish setting[18, 19]. Of the remaining three studies, one was US based and so the costs are unlikely to be transferrable[16] The others were both based within the Spanish healthcare system, which although more potentially relevant to a Scottish NHS perspective, the description of the included cost components and assumptions were not sufficient to allow confirmation of this[7, 11].

None of the studies included an assessment of any of the reported benefits of outpatient biopsy (alongside the costs) compared with OTB, but it may be that the authors' only collected cost information because they perceived the only difference in the procedures to be their comparative costs.

Across the three studies,[11, 18, 19] it is worth noting that the comparative costs of the procedures were not reported because the focus was reimbursement[18], or because the cost was considered to be volume-dependent[19],yet in the study by Saga and colleagues the cost saving associated with outpatient biopsy was stated as €1,631[11]. Where comparative costs were reported[7, 16] the cost of outpatient biopsy was considerably cheaper, at between 5.51% to 22.73% of the cost of OTB.

10. Budget Impact Analysis

As part of the evidence review, SHTG carried out a budget impact analysis from an NHS Scotland perspective. The aim of the analysis was to establish the initial investment cost of

new equipment required to provide outpatient-based biopsies for suspicious laryngeal and/or pharyngeal lesions, and to estimate how much of the initial investment cost can be offset by the potential savings (resource and equipment) associated with conducting these procedures in an outpatient rather than an inpatient or daycase setting - as is currently performed in most NHS Boards at present.

The budget impact analysis is built on the premise that all patients undergo outpatient biopsy for initial investigation. Those who test negative will require OTB to confirm the result. However, owing to the high specificity of the procedure, those who test positive will continue to the next treatment phase, and will therefore not require an OTB. The budget impact analysis seeks to explore the cost impact of outpatient biopsy whilst taking into account a reduction in resources required due to fewer OTBs.

Methods

The following key variables and assumptions were used to inform the budget impact model. Further detail, along with a table including all data used to inform the budget impact analysis, can be found within Appendix 2.

Number of procedures

The number of procedures performed in Scotland was provided by ISD using the OPCS-4 codes for diagnostic laryngoscopy (E36 and E37) and diagnostic pharyngoscopy (E25) (Personal Communication with ISD, 26th June 2018). Not all diagnostic procedures performed will be for suspicious laryngeal and/or pharyngeal lesions, but the relevant proportion was estimated on the basis of clinical advice received, leading to an annual number of patients of 2,264 across Scotland - with lower and upper estimates between 444 and 3,029 patients (Personal Communication with topic referrer, Consultant ENT Surgeon, NHS Greater Glasgow and Clyde, 15 June 2018).

Accuracy of outpatient biopsies

Based on the findings of this Evidence Note, outpatient biopsy procedures are assumed to have a high specificity (0.98). This means that it is rare to get a positive test result in a healthy patient. Therefore, if a positive result is found, then disease is likely, and the patient can move more quickly to appropriate treatment.

The accuracy of outpatient biopsies is expected to reduce the number of patients requiring OTB by 17%

Costs

Equipment and decontamination

Costs were calculated for flexible laryngoscopes, imaging stacks and other peripheral equipment, maintenance contract costs for the laryngoscopes and imaging stack equipment, working channel forceps, decontamination costs and topical anaesthesia.

It was estimated that two new laryngoscopes would need to be purchased by each NHS Board, varied between one and five within the sensitivity analysis. Additional imaging equipment is also required, although NHS Boards may not always need to purchase the imaging and peripheral equipment as they would have access to previously purchased machines used for other outpatient-based endoscopy procedures.

For the laryngoscopes and stack equipment, maintenance and working channel costs were estimated following discussions with each of the manufacturers (Personal Communication with Olympus, 19 July 2018, Personal Communication with Pentax, 19 July 2018, Personal Communication with Karl Storz, 23 July 2018) weighted by their current market share in Scotland (Personal communication with National Services Scotland, 12 December 2017).

The NHS is assumed to incur the cost of annual maintenance for a period of seven years for both the laryngoscope and imaging stack/peripheral imaging equipment. The annual maintenance costs (both for laryngoscopes and imaging stack/peripheral equipment) were varied in sensitivity analysis to account for uncertainty.

Although decontamination costs were included, it was not feasible to include all costs associated with endoscopy decontamination beyond staff costs alone, so the initial investment required for decontamination may be underestimated. However, the approach taken captures the variation in decontamination costs as shown in benchmarking information provided by Health Facilities Scotland (Personal Communication with Health Facilities Scotland, 29 August 2018). Furthermore, by never assuming the outpatient-based procedure has cheaper decontamination costs, a conservative estimate of the overall savings has been sought.

Costs also included the cost of consumables, namely disposable working channel forceps to collect biopsy samples using the laryngoscope equipment, and topical anaesthesia to numb the area before inserting the laryngoscope used for the outpatient procedure.

Resource use

Outpatient biopsies are carried out during an outpatient appointment. It is assumed possible for to be conducted as a daycase procedure in most (96%) of cases, but 15% of patients stay in hospital overnight owing to their individual circumstances rather than any experience of complications during the procedure. All OTB cases will also have had an initial outpatient appointment that did not involve biopsy.

<u>Other assumptions</u>

False positive cases – a proportion of patients (66.7%) were assumed to require further procedures to confirm diagnosis. The budget impact does not account for impact of the patient's well-being following a false positive test.

Tolerability - intolerance of the procedure was assumed to occur in 12.5% of cases. The analysis assumed that between 1% to 25% of patients were required to switch to a day case

procedure, because it was expected that in clinical practice the rate of intolerance may be considerably higher than that found in the literature, where those undergoing the procedure have volunteered to do so.

Complications - the risk of major complications was based on clinical advice about the frequency of oesophageal perforation (1% to 3% of cases) and difficult airway cases (10% to 20%), of which 5% were assumed to require a tracheotomy. The risk of minor complications from outpatient biopsy was assumed to be consistent with the rate found in the literature, i.e. between 0.05% and 2.6%.

Results

Table 2: Results of budget impact analysis

NHS Scotland	Year 1	Year 2	Year 3	Year 4	Year 5	Mean across all five years
Additional investment required to provide outpatient biopsy	£1,465,384	£202,078	£202,078	£202,078	£202,078	£454,739
Net resource savings associated with outpatient biopsy	-£589,442	£673,865	£673,865	£673,865	£673,865	£421,204
Overall cost of outpatient biopsy	£4,743,116	£3,479,809	£3,479,809	£3,479,809	£3,479,809	£3,732,470
Overall cost of current practice	£4,153,674	£4,153,674	£4,153,674	£4,153,674	£4,153,674	£4,153,674

The results of the budget impact analysis show that the initial additional investment required across NHSScotland is approximately £1,465,384 in the first year, and £202,078 in subsequent years. Over the first five years the mean annual investment required is £454,739. However, once the potential annual savings associated with being able to provide procedure in an outpatient, rather than inpatient or daycase setting, are taken into account, the net cost to NHSScotland in the first year falls to £589,442 and in each of the subsequent four years there is a net resource saving of £673,865. Therefore, over five years NHSScotland can expect to achieve on average an annual resource saving of £421,204.

11. Conclusion

Most studies of outpatient biopsy were retrospective and none of the diagnostic test accuracy studies comparing with OTB used the most up to date imaging technology. Sensitivity and specificity in the largest prospective study were typical of the evidence base overall at 71% and 97% respectively for identifying malignancy in patients with suspicious laryngeal and pharyngeal lesions when compared with the gold standard of OTB. Outpatient biopsy has good ability to rule in malignancy in patient groups where there is strong clinical suspicion, meaning that selected patients may avoid OTB. Two studies offer evidence that this shortens time to diagnosis or time to treatment. Outpatient biopsy appears to be safe and is well tolerated by most patients. Although the current published evidence base does not contain sufficient evidence on the cost-effectiveness of outpatient biopsy, where costs had been reported the procedure was shown to be considerably lower than operating theatre biopsy. A budget impact analysis for NHS Scotland indicates that introducing outpatient biopsy is likely to be cost-saving over five years. Accounting for initial investment costs, the average resource saving per annum over five years is expected to be in excess of £400,000 for NHSScotland.

12. Identified research gaps

A large prospective study identifying patients' experiences, examining sensitivity and specificity where enhanced imaging technology is incorporated and including a detailed cost assessment would add to the evidence base.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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Declarations of interest were sought from all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

Healthcare Improvement Scotland development team

- Lorna Thompson, Lead Author/Health Services Researcher
- Jenni Hislop, Senior Health Economist
- Members of the SHTG Evidence Review Committee

Appendix 1: definitions of diagnostic accuracy terms

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease[20].

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease[20].

Positive likelihood ratio: the probability that a positive test result will occur in a person with the target condition divided by the probability of a positive test result occurring in a person without the disease, that is the sensitivity divided by one minus specificity[20].

Negative likelihood ratio: the probability that a negative test result will occur in a person with the target condition divided by the probability of a negative test result occurring in a person without the disease, that is the 1-sensitivity divided by specificity[20].

Receiver operating characteristic (ROC) curve: a graph used to assess the ability of a diagnostic test to discriminate between people with or without the target condition. For most diagnostic test data the ROC curve plots sensitivity against 1-specificity for different cut-off values[20]. Area under the ROC curve (AUROC) can be used to compare the diagnostic accuracy of tests when multiple ROC curves are plotted on the same graph.

Appendix 2: Budget Impact Analysis

A budget impact analysis was carried out from an NHS Scotland perspective to establish the initial investment cost of new equipment required to provide outpatient-based biopsies for suspicious laryngeal and/or pharyngeal lesions, and to estimate how much of the initial investment cost can be offset by the potential savings (resource and equipment) associated with conducting these procedures in an outpatient rather than an inpatient/daycase setting - as is currently performed in most NHS Boards at present.

The budget impact analysis is built on the premise that patients undergo outpatient biopsy for initial investigation. Owing to the high specificity of the procedure, those who test positive will continue to the next treatment phase, whilst those that test negative will require OTB to confirm the result. The budget impact analysis seeks to explore the cost impact of outpatient biopsy whilst taking into account a reduction in resources required due to fewer OTBs.

Methods

The data used to inform the budget impact analysis are provided in Table 2. A base case analysis was undertaken with a one-way sensitivity analysis to account for uncertainty in parameters. However, as there were a range of parameters for which there was greater uncertainty, probability distributions were also applied to these data to try to ensure estimates would be sufficiently robust. Distribution information is provided in Table 3.

Table 3: Input parameter values for Budget Impact Analysis

Item	Base case value	Lower bound value	Upper bound value	Source
Imaging stack plus peripherals etc - Life Expectancy of the technology (years)	10	7	13	Discussion with NSS/ Manufacturer
Laryngoscope - Life Expectancy of the technology (years)	10	7	13	Discussion with NSS/ Manufacturer
Number of laryngoscopes needed per board	2	1	5	Clinical advice/ Assumption
Proportion of laryngoscope purchases needed where an existing imaging stack is already available	0.125	0.000	1.000	Assumption
Imaging stack plus peripherals price per device(s) (GBP)	Commercial in confidence			Discussion with NSS/ Manufacturer
Laryngoscope price per device (GBP)	Commercial in confidence			Discussion with NSS/ Manufacturer
Working channel forceps price per outpatient biopsy (GBP)	Commercial in confidence			Discussion with NSS/ Manufacturer
Imaging stack plus peripherals, price per annum for maintenance	Commercial in confidence			Discussion with NSS/ Manufacturer
Laryngoscope price per annum for maintenance	Commercial in confidence			Discussion with NSS/ Manufacturer
Topical anaesthesia cost per outpatient biopsy	£9.69	£0.00	£12.90	BNF
Annual number of patients expected	2,264	444	3029	Clinical advice/ ISD data

Item	Base case value	Lower bound value	Upper bound value	Source
Average cost per outpatient visit (GBP)	£123	£81	£167	ISD
Average cost per daycase visit (GBP)	£1431	£847	£1887	ISD
Cost per inpatient visit (GBP)	£2657	£1849	£2874	ISD
Additional time required to perform outpatient biopsy (minutes)	15	0	45	Clinical advice/ Assumption
Cost per additional minute required for a consultant's time (GBP)	£1.78	Not varied in sensitivity analysis		PSSRU
Additional staff member cost per outpatient biopsy (GBP)	£0.62	£0.00	£1.78	Clinical advice/ PSSRU
Additional decontamination cost per outpatient biopsy (GBP)	£23.08	£0.00	£35.45	Clinical advice/ PSSRU
Cost per additional bed day (GBP)	£1366	£1042	£1621	Calculated from ISD data
Estimated number of additional bed days for inpatient/daycase minor complications	1	0	2	Clinical advice/ Assumption
Estimated number of additional bed days for inpatient/daycase major complications	6	2	14	Clinical advice/ Assumption

Item	Base case value	Lower bound value	Upper bound value	Source
Probability of disease being present among population attending for suspicious laryngeal/pharngeal lesions	0.306	0.270	0.352	ISD Cancer Incidence Data/ Assumption
Sensitivity (Probability of True Positive)	0.760	0.60	0.811	Evidence Note
Specificity (Probability of True Negative)	0.978	0.87	1.00	Evidence Note
Probability of outpatient complications and intolerance of the procedure requiring conversion/reschedule to a daycase procedure	0.134	0.06	0.27	Evidence Note
Probability of major daycase complications	0.027	0.015	0.040	Discussion
Probability of minor daycase complications (not including dental problems)	0.01	0.005	0.026	Evidence Note/ Assumption
Probability of overnight stay due to patient circumstances	0.15	0.075	0.225	Clinical advice

Table 4: Distributions used for probabilistic sensitivity analysis (PSA)

Item	Distribution (α, β, minimum, maximum)
Imaging stack plus peripherals etc - Life expectancy of the technology (years)	Beta (3.5, 3.5, 7, 13)
Laryngoscope - Life Expectancy of the technology (years)	Beta (3.5, 3.5, 7, 13)
Number of laryngoscopes needed per board	Beta (1.6667, 3.3333, 1, 5)
Proportion of laryngoscope purchases needed where an existing imaging stack is not also needed (as already available)	Beta (0.6875, 2.0625, 0, 1)
Imaging stack plus peripherals price per device(s) (GBP)	Commercial in Confidence
Laryngoscope price per device (GBP)	Commercial in Confidence
Working channel forceps price per outpatient biopsy (GBP)	Commercial in Confidence
Imaging stack plus peripherals, price per annum for maintenance	Commercial in Confidence
Laryngoscope price per annum for maintenance	Commercial in Confidence
Topical anaesthesia cost per outpatient biopsy	Beta (4.3333, 2.1634, 0, 12.9)
Annual number of patients expected	Beta (4.3006, 2.4609, 444, 3029)
Average cost per outpatient visit (GBP)	Beta (3.4292, 3.5372, 81, 167)
Average cost per daycase visit (GBP)	Beta (3.8365, 3.2546, 847, 1887)
Cost per inpatient visit (GBP)	Beta (4.3092, 1.9163, 1849, 2874)
Additional time required to perform outpatient biopsy (minutes)	Beta (2.3272, 3.6570, 0, 45)

Item	Distribution (α, β, minimum, maximum)
Cost per additional minute required for a consultant's time (GBP)	Not varied in PSA
Additional staff member cost per outpatient biopsy (GBP)	Beta (2.4237, 3.6782, 0, 1.783)
Additional decontamination cost per outpatient biopsy (GBP)	Beta (4.1870, 2.7832, 0, 35.45)
Cost per additional bed day (GBP)	Beta (3.8269, 3.2635, 1042, 1621)
Estimated number of additional bed days for inpatient/daycase minor complications	Beta (3.5, 3.5, 0, 2)
Estimated number of additional bed days for inpatient/daycase major complications	Beta (2.9506, 3.6883, 2, 14)
Prevalence of disease among population attending for suspicious laryngeal/pharngeal lesions	Beta (3.0758, 3.6643, 0.2703, 0.3518)
Sensitivity (Probability of True Positive)	Beta (4.3306, 2.0817, 0.6, 0.811)
Specificity (Probability of True Negative)	Beta (4.2233, 1.6382, 0.87, 1)
Probability of outpatient complications and intolerance of the procedure requiring conversion/reschedule to a daycase procedure	Beta (2.4743, 3.6870, 0.06, 0.27)
Probability of major daycase complications	Beta (3.3769, 3.5619, 0.015, 0.04)
Probability of minor daycase complications (not including dental problems)	Beta (1.5715, 3.2579, 0.005, 0.026)
Probability of overnight stay due to patient circumstances	Beta (3.5, 3.5, 0.075, 0.225)

To quantify the budget impact associated with conducting outpatient-based biopsies for laryngeal and/or pharyngeal lesions, the costs associated with current clinical practice in Scotland, where most procedures are conducted in a daycase setting, were compared with the costs likely to be associated with conducting procedures in an outpatient setting. The diagnostic accuracy of the outpatient-based procedure was taken from the clinical effectiveness evidence identified in this review. Given the sensitivity results reported, the analysis assumes that all patients testing negative for the outpatient procedure would still need this confirmed by the daycase procedure. However, owing to the high specificity of the procedure, for positive cases treatment could begin without the need for a confirmation biopsy.

For the small number of false positive cases, there is still some uncertainty as to how these patients would have their diagnosis corrected in clinical practice. To account for this, it was therefore assumed that 33% would receive (and therefore costs would be incurred for) the daycase procedure, 33% would receive a second outpatient-based procedure (which was assumed not to yield another false positive result that would necessitate a third procedure) and another 33% would have their diagnosis corrected spontaneously upon further planning for cancer treatment using other methods outwith the scope of this budget impact analysis. It was assumed that no patient would undergo treatment for a cancer that was based on a false positive biopsy result. However, it is important to note that there may be a considerable impact on the patient's well-being resulting from a false positive result. While it was not possible to incorporate this within a budget impact analysis, it is assumed that in clinical practice staff would be aware of the possibility of a false positive diagnosis and it could be corrected quickly following the outpatient-based procedure so as to minimise the distress to the patient.

It was also assumed that the outpatient-based procedure would not be able to be tolerated by all patients, and that complications could arise during an outpatient procedure requiring a switch to a daycase procedure. In these cases, the costs of both the outpatient and daycase-based procedures were incurred as the former had been attempted but the latter also had to be provided. Outpatient complications were assumed to occur within a range of between 0.05% and 2.6% of cases, based on the evidence note, whereas intolerance of the procedure was assumed to affect on average 12.5% of cases. The range was varied between 1% to 25% of patients as it was expected that in clinical practice the rate of intolerance may be considerably higher than that found in the literature, where those undergoing the procedure have volunteered to do so.

For each daycase procedure undertaken, there was a risk of complications (e.g. oesophageal perforation or the need for the patient to have a tracheotomy) or the need for a patient to stay overnight based on their circumstances (e.g. the patient's age and/or if they lived alone). Assuming no complications, the cost of an average ENT inpatient stay was used to account for overnight stays due to patient circumstances. Complications could be either

minor (incurring the possibility of between zero to two nights in hospital) or major (between two to fourteen nights in hospital). The risk of major complications was based on clinical advice about the frequency of oesophageal perforation (1% to 3% of cases) and difficult airway cases (10% to 20%), of which 5% were assumed to require a tracheotomy. The risk of minor complications from outpatient biopsy was assumed to be consistent with the rate found in the literature, i.e. between 0.05% and 2.6%. This did not include the cost of dental work required by patients as the frequency of these events was unclear in terms of both self- or hospital initiated referral and self-funding by patients as opposed to compensation by the NHS Board for the inconvenience. While this is a limitation, it is expected to lead to a more conservative estimate of the savings associated with outpatient biopsy given that dental work is more likely to be required after the daycase compared with the outpatient setting.

In terms of equipment, it was estimated that between one and five new laryngoscopes would need to be purchased by each NHS Board. Additional imaging equipment is also required. However, as this imaging equipment can also be used for other endoscope procedures in other specialties, it was assumed that for one in every eight laryngoscopes required, the NHS Board would not need to purchase the imaging and peripheral equipment as they would have access to previously purchased machines used for other outpatient-based endoscopy procedures.

The NHS incurs the cost of annual maintenance for a period of seven years for both the laryngoscope and imaging stack/peripheral imaging equipment. Some maintenance contracts may be longer or shorter, and some NHS Boards may prefer to arrange their own maintenance outwith a contract with the manufacturer of the technology. The annual maintenance costs (both for laryngoscopes and imaging stack/peripheral equipment) were varied in sensitivity analysis to account for some of the uncertainty, although different contract lengths will affect when the impact to the budget occurs. Beyond the timeframe of the maintenance contract, both the laryngoscope and imaging stack/peripheral technology has a limited life-expectancy of up to 13 years, whereupon replacement would be needed.

Peripheral costs did not include the cost of consumables, namely disposable working channel forceps to collect biopsy samples and topical anaesthesia. Nor did they include the potential additional costs of decontamination. Decontamination costs were estimated based on the staff resource use associated with processing single endoscopes within an endoscopy decontamination unit (for flexible laryngoscopes) or central sterilisation services (for rigid laryngoscopes), following discussions with staff working in these departments and at Health Facilities Scotland (Personal Communication with Health Facilities Scotland, 1 August 2018, Personal Communication with NHS Greater Glasgow and Clyde, 1 August 2018, Personal Communication with NHS Ayrshire and Arran, 1 August 2018).

The number of procedures performed in Scotland was requested from ISD using the OPCS-4 codes for diagnostic laryngoscopy (E36 and E37) and diagnostic pharyngoscopy (E25) (Personal Communication with ISD, 26th June 2018). Not all diagnostic procedures

performed will be for suspicious laryngeal and/or pharyngeal lesions, but the relevant proportion was estimated on the basis of clinical advice received, leading to variation in the annual number of patients seen between 444 and 3,029 patients (Personal Communication with topic referrer, Consultant ENT Surgeon, NHS Greater Glasgow and Clyde, 15 June 2018).

The incidence of laryngeal and pharyngeal cancer is available for the general population[20] However, the rate was expected to be much higher for those being seen in clinical practice because of suspicious laryngeal and/or pharyngeal lesions. Therefore, the numbers diagnosed each year in Scotland were divided by the number of procedures estimated to be being performed each year in Scotland for the diagnosis of suspicious lesions.

Costs were calculated separately for flexible laryngoscopes, imaging stacks and other peripheral equipment, maintenance contract costs for the laryngoscopes and imaging stack equipment, working channel forceps, decontamination costs and topical anaesthesia. For the laryngoscopes and stack equipment, maintenance and working channel costs were estimated following discussions with each of the manufacturers (Personal Communication with Olympus, 19 July 2018, Personal Communication with Pentax, 19 July 2018, Personal Communication with Karl Storz, 23 July 2018) weighted by their current market share in Scotland (Personal communication with National Services Scotland, 12 December 2017)

The cost of topical anaesthesia was taken from the BNF cost for lidocaine with phenylephrine, assuming that some patients would already receive topical anaesthsia in clinical practice to numb the area before viewing the lesions with a laryngoscope that does not have a working channel. Therefore the added cost for topical anaesthesia was estimated to be between zero and £12.90 per patient[21].

The additional time required to conduct an outpatient-based biopsy beyond the current outpatient procedure was assumed to range between zero and 45 minutes. Based on discussions with clinicians, costs were included for a consultant's time and an additional staff member's time as more than one person is required to be present with the patient during the procedure (Personal Communication with topic referrer, Consultant ENT Surgeon, NHS Greater Glasgow and Clyde, 15 June 2018). The unit costs of staff time were taken from the PSSRU Unit Costs of Health and Social Care 2017[22]. The average cost was taken to be a band 5 nurse, but it was recognised that the range in unit cost for this additional person may be considerable.

For decontamination costs, PSSRU costs for Agenda for Change Band 2 personnel were used for proposed endoscopy decontamination of flexible laryngoscopes - following input from clinicians and local staff working in decontamination - and the total decontamination cost was based on the number of pieces of endoscopic equipment decontaminated per day inclusive of the risk of decontamination failure which would require the process to start again (Personal Communication with NHS Greater Glasgow and Clyde, 1 August 2018).

It is a limitation of our analysis that it was not feasible to include all costs associated with endoscopy decontamination rather than staff costs alone within the timeframe, and so the initial investment required for decontamination may be underestimated. Costs for central sterilisation services to process theatre equipment are already included in the theatre costs associated with the inpatient and daycase procedure costs as calculated by ISD and it was not possible to subtract a proportion of the Central Sterile Supply Department (CSSD) costs included in these data but it was possible to estimate the total staff costs for the department and divide this by the estimated number of instrument trays processed per week, to get the average unit cost per processed tray (Personal Communication with NHS Ayrshire and Arran, 1st August 2018). The difference in costs was varied in sensitivity analyses from zero (i.e. decontamination costs are equivalent for these procedures) to being £35.45 per procedure more expensive for the outpatient-based biopsy. These data acknowledge the variation in decontamination costs as shown by benchmarking information provided by Health Facilities Scotland (Personal Communication with Health Facilities Scotland, 29 August 2018). It is assumed that by never assuming the outpatient-based procedure has cheaper decontamination costs, a conservative estimate of the savings associated with performing the procedure in the outpatient setting can be obtained.

The costs of the outpatient-based, daycase based and inpatient-based (where required) procedures were taken from the average ENT speciality costs for each of these procedures, varied in sensitivity analysis to account for differences in average costs between NHS Boards. A gross cost per additional bed day was used to quantify the cost associated with complications, based on length of stay expected for each type of complication[23].

Results

The base case results (Table 5) indicate that, in order to provide an outpatient biopsy service, the NHS would have to invest £1,333,044 in the first year, reducing to £205,940 in years 2 to 5. However, the annual resource savings estimated from obtaining a positive diagnosis for patients in an outpatient rather than an inpatient/daycase setting means the net cost in the first year would be £684,203, as £648,841 (48.7%) of the initial investment would be offset in the first year alone by resource savings associated with implementation of the outpatient-based procedure.

Results were varied in a one-way sensitivity analysis to account for uncertainties in the parameters used to calculate the budget impact. Means and standard deviations are provided in Table 5, but to further illustrate the range of results, in the first year, the net expected interquartile range of savings is -£514,232 and -£830,315 (i.e. the initial investment is not expected to be recovered in the first year). The interquartile range of savings in subsequent years where technology investment/replacement is not expected to occur, is between £348,035 and £512,932. When parameters were varied in the one-way sensitivity analysis, the extent to which annual savings were sensitive to the input parameters was most pronounced for the number of laryngoscopes required, expected patient numbers, disease incidence and procedure costs.

Of note is that the base case analysis estimates around 83% of people will end up receiving inpatient/daycase treatment. This is largely due to the estimated disease prevalence among the population of interest and current available evidence on the diagnostic accuracy of outpatient biopsy that does not account for enhanced imaging. At present, this would necessitate confirmation that those testing negative upon outpatient biopsy are true negative results, by obtaining an additional biopsy sample using the daycase procedure. The potential saving to be made if it would be possible to extend outpatient-only biopsy without a need to provide confirmation testing to those who test negative is estimated at £2,655,906 in the first year alone. This is likely to exceed the costs that would be anticipated from conducting a further study to explore the comparative diagnostic accuracy of these procedures with enhanced imaging. Nevertheless, the implications of misdiagnosis (false negative and false positive results) may incur additional costs that it was not possible to include in this analysis, and so further research on the diagnostic accuracy may be warranted.

Probabilistic sensitivity analysis was conducted to consider the combined effect of uncertainty in the parameters using the distributions listed in Table 4. The effect across 1,000 iterations shows the initial investment range to be similar to the base case with a mean (SD) investment of £1,465,384 (£538,307) and a net cost of £589,442 (£572,378) in year 1 once the difference in the costs of undertaking each procedure is considered. However, for years 2 to 5, the expected median (IQR) saving per annum is £673,865 (£193,791) A comparison of the values for the initial base case and one-way sensitivity analysis and the probabilistic results is show in Table 5.

Table 5: Mean (SD) results from Budget Impact Analyses for the first five years following implementation

NHS Scotland	Year 1 Mean (SD)	Year 2 Mean (SD)	Year 3 Mean (SD)	Year 4 Mean (SD)	Year 5 Mean (SD)	Mean (SD) across all five years
Base case gross cost	£1,333,044	£205,940	£205,940	£205,940	£205,940	£431,361
Base case net cost	£684,203	-£442,901	-£442,901	-£442,901	-£442,901	-£217,480
One-way sensitivity analysis Gross cost	£1,446,153 (£701,050)	£192,606 (£55,029)	£192,606 (£55,029)	£192,606 (£55,029)	£192,606 (£55,029)	£443,316 (£560,603)
One-way sensitivity analysis Net cost	£753,480 (£1,203,465)	-£500,066 (£650,763)	-£500,066 (£650,763)	-£500,066 (£650,763)	-£500,066 (£650,763)	-£249,356 (£742,899)
Probabilistic sensitivity analysis Gross cost	£1,465,384 (£538,307)	£202,078 (£64,123)	£202,078 (£64,123)	£202,078 (£64,123)	£202,078 (£64,123)	£454,739 (£126,709)
Probabilistic sensitivity analysis Net cost	£589,442 (£572,378)	-£673,865 (£193,791)	-£673,865 (£193,791)	-£673,865 (£193,791)	-£673,865 (£193,791)	-£421,204 (£224,481)

It is likely that all these values are conservative estimates, given the caution applied when determining the input values. Local estimates for each NHS Board area are provided in Appendix 3, based on expected numbers of patients being seen in clinical practice. If NHS staff wish to receive additional detail, or have estimated their own parameters for use with these calculations instead of those described in Table 3, please contact SHTG using the details provided at the end of this Evidence Note.

Appendix 3: Budget Impact Analysis Results for NHS Board areas

NHS Ayrshire and Arran	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£83,021	£12,826	£12,826	£12,826	£12,826	£26,865
Base case net cost	£42,612	-£27,583	-£27,583	-£27,583	-£27,583	-£13,544
One-way sensitivity analysis Gross cost	£90,065	£11,995	£11,995	£11,995	£11,995	£27,609
One-way sensitivity analysis Net cost	£46,926	-£31,144	-£31,144	-£31,144	-£31,144	-£15,530
Probabilistic sensitivity analysis Gross cost	£91,263	£12,585	£12,585	£12,585	£12,585	£28,321
Probabilistic sensitivity analysis Net cost	£36,710	-£41,968	-£41,968	-£41,968	-£41,968	-£26,232

NHS Borders	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£19,430	£3,002	£3,002	£3,002	£3,002	£6,288
Base case net cost	£9,973	-£6,456	-£6,456	-£6,456	-£6,456	-£3,170
One-way sensitivity analysis Gross cost	£21,079	£2,807	£2,807	£2,807	£2,807	£6,462
One-way sensitivity analysis Net cost	£10,983	-£7,289	-£7,289	-£7,289	-£7,289	-£3,635
Probabilistic sensitivity analysis Gross cost	£21,359	£2,945	£2,945	£2,945	£2,945	£6,628
Probabilistic sensitivity analysis Net cost	£8,592	-£9,822	-£9,822	-£9,822	-£9,822	-£6,139

NHS Dumfries and Galloway	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£41,216	£6,367	£6,367	£6,367	£6,367	£13,337
Base case net cost	£21,155	-£13,694	-£13,694	-£13,694	-£13,694	-£6,724
One-way sensitivity analysis Gross cost	£44,713	£5,955	£5,955	£5,955	£5,955	£13,707
One-way sensitivity analysis Net cost	£23,297	-£15,461	-£15,461	-£15,461	-£15,461	-£7,710
Probabilistic sensitivity analysis Gross cost	£45,308	£6,248	£6,248	£6,248	£6,248	£14,060
Probabilistic sensitivity analysis Net cost	£18,225	-£20,835	-£20,835	-£20,835	-£20,835	-£13,023

NHS Fife	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£61,235	£9,460	£9,460	£9,460	£9,460	£19,815
Base case net cost	£31,430	-£20,345	-£20,345	-£20,345	-£20,345	-£9,990
One-way sensitivity analysis Gross cost	£66,431	£8,848	£8,848	£8,848	£8,848	£20,364
One-way sensitivity analysis Net cost	£34,612	-£22,971	-£22,971	-£22,971	-£22,971	-£11,455
Probabilistic sensitivity analysis Gross cost	£67,314	£9,283	£9,283	£9,283	£9,283	£20,889
Probabilistic sensitivity analysis Net cost	£27,077	-£30,955	-£30,955	-£30,955	-£30,955	-£19,349

NHS Forth Valley	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£30,029	£4,639	£4,639	£4,639	£4,639	£9,717
Base case net cost	£15,413	-£9,977	-£9,977	-£9,977	-£9,977	-£4,899
One-way sensitivity analysis Gross cost	£32,577	£4,339	£4,339	£4,339	£4,339	£9,986
One-way sensitivity analysis Net cost	£16,973	-£11,265	-£11,265	-£11,265	-£11,265	-£5,617
Probabilistic sensitivity analysis Gross cost	£33,010	£4,552	£4,552	£4,552	£4,552	£10,244
Probabilistic sensitivity analysis Net cost	£13,278	-£15,180	-£15,180	-£15,180	-£15,180	-£9,488

NHS Grampian	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£60,058	£9,278	£9,278	£9,278	£9,278	£19,434
Base case net cost	£30,825	-£19,954	-£19,954	-£19,954	-£19,954	-£9,798
One-way sensitivity analysis Gross cost	£65,154	£8,677	£8,677	£8,677	£8,677	£19,973
One-way sensitivity analysis Net cost	£33,947	-£22,529	-£22,529	-£22,529	-£22,529	-£11,234
Probabilistic sensitivity analysis Gross cost	£66,020	£9,104	£9,104	£9,104	£9,104	£20,487
Probabilistic sensitivity analysis Net cost	£26,556	-£30,360	-£30,360	-£30,360	-£30,360	-£18,977

NHS Greater Glasgow and Clyde	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£536,397	£82,867	£82,867	£82,867	£82,867	£173,573
Base case net cost	£275,313	-£178,217	-£178,217	-£178,217	-£178,217	-£87,511
One-way sensitivity analysis Gross cost	£581,911	£77,502	£77,502	£77,502	£77,502	£178,384
One-way sensitivity analysis Net cost	£303,189	-£201,219	-£201,219	-£201,219	-£201,219	-£100,337
Probabilistic sensitivity analysis Gross cost	£589,649	£81,313	£81,313	£81,313	£81,313	£182,980
Probabilistic sensitivity analysis Net cost	£237,183	-£271,153	-£271,153	-£271,153	-£271,153	-£169,486

NHS Highland	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£74,778	£11,552	£11,552	£11,552	£11,552	£24,197
Base case net cost	£38,381	-£24,845	-£24,845	-£24,845	-£24,845	-£12,200
One-way sensitivity analysis Gross cost	£81,123	£10,804	£10,804	£10,804	£10,804	£24,868
One-way sensitivity analysis Net cost	£42,267	-£28,051	-£28,051	-£28,051	-£28,051	-£13,988
Probabilistic sensitivity analysis Gross cost	£82,201	£11,336	£11,336	£11,336	£11,336	£25,509
Probabilistic sensitivity analysis Net cost	£33,065	-£37,801	-£37,801	-£37,801	-£37,801	-£23,628

NHS Lanarkshire	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£115,994	£17,920	£17,920	£17,920	£17,920	£37,535
Base case net cost	£59,535	-£38,539	-£38,539	-£38,539	-£38,539	-£18,924
One-way sensitivity analysis Gross cost	£125,836	£16,759	£16,759	£16,759	£16,759	£38,575
One-way sensitivity analysis Net cost	£65,563	-£43,513	-£43,513	-£43,513	-£43,513	-£21,697
Probabilistic sensitivity analysis Gross cost	£127,509	£17,584	£17,584	£17,584	£17,584	£39,569
Probabilistic sensitivity analysis Net cost	£51,290	-£58,636	-£58,636	-£58,636	-£58,636	-£36,651

NHS Lothian	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£213,735	£33,020	£33,020	£33,020	£33,020	£69,163
Base case net cost	£109,702	-£71,013	-£71,013	-£71,013	-£71,013	-£34,870
One-way sensitivity analysis Gross cost	£231,870	£30,882	£30,882	£30,882	£30,882	£71,079
One-way sensitivity analysis Net cost	£120,810	-£80,178	-£80,178	-£80,178	-£80,178	-£39,981
Probabilistic sensitivity analysis Gross cost	£234,953	£32,400	£32,400	£32,400	£32,400	£72,911
Probabilistic sensitivity analysis Net cost	£94,509	-£108,045	-£108,045	-£108,045	-£108,045	-£67,534

NHS Orkney	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£589	£91	£91	£91	£91	£191
Base case net cost	£302	-£196	-£196	-£196	-£196	-£96
One-way sensitivity analysis Gross cost	£639	£85	£85	£85	£85	£196
One-way sensitivity analysis Net cost	£333	-£221	-£221	-£221	-£221	-£110
Probabilistic sensitivity analysis Gross cost	£647	£89	£89	£89	£89	£201
Probabilistic sensitivity analysis Net cost	£260	-£298	-£298	-£298	-£298	-£186

NHS Tayside	Year 1	Year 2	Year 3	Year 4	Year 5	Mean average across 5 years
Base case gross cost	£95,386	£14,736	£14,736	£14,736	£14,736	£30,866
Base case net cost	£48,958	-£31,692	-£31,692	-£31,692	-£31,692	-£15,562
One-way sensitivity analysis Gross cost	£103,479	£13,782	£13,782	£13,782	£13,782	£31,721
One-way sensitivity analysis Net cost	£53,915	-£35,782	-£35,782	-£35,782	-£35,782	-£17,843
Probabilistic sensitivity analysis Gross cost	£104,855	£14,460	£14,460	£14,460	£14,460	£32,539
Probabilistic sensitivity analysis Net cost	£42,177	-£48,218	-£48,218	-£48,218	-£48,218	-£30,139

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