

National Institute for Health and Clinical Excellence

**Patient safety and reduction of risk of transmission of Creutzfeldt–
Jakob disease (CJD) via interventional procedures**

**Report
ScHARR**



**The
University
Of
Sheffield.**



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Executive Summary

Following an operation on a patient incubating vCJD or CJD (the abbreviation CJD will henceforth be used for both vCJD and CJD) who has reached the infectious period, the surgical instruments used will have harvested infectious mass. Current decontamination procedures do not completely remove or de-activate this infectious mass and thus subsequent patients are at risk of iatrogenic infection and death. This report focuses on the cost-effectiveness of single-use surgical instruments, which by definition will eliminate the risk of iatrogenic infection through contaminated surgical instruments.

The analysis below accounts for costs and benefits over a period of 5 years, as expert advisors believe that an effective decontamination intervention will be available at the end of that time. The analysis is based upon a discrete event simulation model that models patients arriving for operations, their CJD status, and the use and cleansing of surgical instruments. Patients that carry sub-clinical CJD, may contaminate the surgical instruments, and result in transmission to patients during further surgery with those instruments.

The parameters of the model were taken from the literature where possible. However a number of key parameters, such as the prevalence of CJD, or the effectiveness of current decontamination procedures in removing or deactivating infectious mass, could not be sourced from the literature. These parameters were populated via elicitation sessions with experts nominated by NICE who were willing to participate. Given the large uncertainty associated with these distributions, probabilistic sensitivity analyses were undertaken.

Initial analyses showed that only operation sites with an infectious titre of 6 log or greater were at risk of a significant number of iatrogenic deaths, and that all other sites had prohibitively large cost per Quality Adjusted Life Year (QALY) associated with the introduction of single-use instruments.

For the remaining 'high risk' specialties (neurosurgery, posterior eye surgery and neuroendoscopy), analyses were conducted to assess the effects of (i) instrument migration and (ii) targeting patients with previous 'high-risk' surgery. Instrument migration denotes that during the cycle of use in an operation, subsequent decontamination or storage, instruments may become detached from the set to become part of an additional set or become a supplementary instrument, with a similar instrument replacing it in the original set.

The cost-effectiveness of targeting single-use instruments at those patients with a history of 'high risk' surgery was evaluated as these patients have had a possibility of being infected during the previous surgery, and may be at a higher risk of incubating CJD than similar patients who have not had a 'high risk' surgical procedure.

Eliminating instrument migration significantly reduces the risk of iatrogenic transmission of CJD. Assuming that instrument migration can be prohibited then the mean cost per QALY of single-use instruments for those patients with previous 'high risk' surgery was £45k for posterior eye surgery, £99k for brain surgery, and £252k for spinal cord surgery, although these all have wide confidence intervals. If instrument migration continues at the presently estimated rates these mean values fall to £4k, £19k and £352k respectively due to a greater number of deaths. These results

made CJDAS produce guidance that instrument migration must be prohibited in ‘high risk’ surgery, whether through the purchasing of additional equipment so that supplementary items are no longer needed, through more diligent implementation of procedures, or through commercial computerised tracking products. Assuming this was achieved, CJDAS decided that the introduction of single-use instruments was not cost-effective in neurosurgery or posterior eye operations.

Neuroendoscopy was analysed separately as this involves both a neuroendoscope and separate accessories, and the risk of iatrogenic infection is removed only when both are made single-use. Single-use accessories can still infect subsequent patients through gathering infectious mass contained in a lumen of a neuroendoscope, and more complex analyses were required. Neuroendoscopes have 2 types, rigid neuroendoscopes, which can be autoclaved, and more expensive flexible neuroendoscopes, which cannot. Analyses showed that for both types, single-use neuroendoscopes were not cost-effective. Single-use accessories were associated with cost per QALYs of £15k for rigid neuroendoscopes and £22k for flexible neuroendoscopes. Both values were considered to be cost-effective and CJDAS recommended the introduction of single-use accessories for neuroendoscopy. These cost per QALY values are also likely to be decreased, should the cost of single-use accessories decrease following mass production, as has been observed with general endoscopy accessories.

The recommendation of the introduction of single-use accessories in neuroendoscopy only is associated with an estimated cost of £712k in the UK over a 5-year period. This cost will be reduced should the price of neuroendoscopy accessories decrease.

1 Background to the report

Rationale for the work.

The Chief Medical Officer asked the National Institute for Health and Clinical Excellence (NICE) to develop and publish guidance to the NHS on how best to manage the risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) during surgical procedures. To fulfil this task, an independent committee, the CJD Advisory Sub-Committee (CJDAS) was established to advise NICE through the Interventional Procedures Advisory Committee. This committee would provide guidance on surgical practice and the choice of instruments when involving tissue that could have high or medium infectious titre of CJD or vCJD.

Additionally, NICE invited tenders from third parties to review the published literature and to build a decision analytical model to estimate the potential number of surgical secondary CJD infections, and the cost-effectiveness of policies aimed at reducing the risk of infection.

The School of Health and Related Research (ScHARR) won this tender. We have produced two reports. This report focuses primarily on modelling the costs and effectiveness of policies aimed at minimising the risks of CJD transmission during surgery. The balance between the expected number of cases of iatrogenic CJD avoided and the additional direct medical costs of single-use instruments is explored within this report. A second report focuses on the data found from our literature review. The second report provided little directly usable information for modelling purposes.

Background to CJD.

CJD is a progressive, fatal neurological disease that belongs to a wider group of neurodegenerative disorders, the transmissible spongiform encephalopathies (TSEs), or prion diseases. Historically there have been three classes of CJD;

- sporadic, which is the most common, has an unknown aetiology, is found in all countries and has an annual incidence of 1 in a million;
- inherited (familial), and
- iatrogenic, which is caused by exposure to CJD prions in a medical or surgical procedure.

In most cases CJD affects people aged 60 years or older.

Since 1995 vCJD has also been characterised, with the cause widely believed to have been through eating meat contaminated with bovine spongiform encephalopathy. This has definitely or probably resulted in 153 deaths up to 2006. Similarly to CJD, vCJD is a progressive, fatal neurological disease, but has a much younger age at onset, having a mean age of death of 28 years. Whilst measures have been introduced to minimise the risks of infected meat entering the food chain, there is much uncertainty regarding the prevalence of vCJD in people yet to exhibit clinical symptoms. These people could contaminate surgical instruments, which then could iatrogenically infect surgical patients.

The genotype of a patient at codon 129 can affect both the likelihood of contracting clinical CJD and the time before clinical symptoms occur. Three genotypes exist at codon 129, m-m, m-v and v-v, which are estimated to be 40%, 50% and 10% of the UK population respectively. All clinical cases of vCJD from primary (dietary) infection have been of the m-m genotype at codon 129. However it is uncertain whether this is because the remaining genotypes were less susceptible to dietary infection, whether the incubation period before clinical symptoms become apparent is of a longer duration in these genotypes, or a combination of both factors.

For the purposes of readability the term CJD will be used forthwith to encompass both CJD and vCJD.

Background to the potential risks associated with re-usable surgical instruments

The transfer of prions from an infected patient to surgical instruments, and from surgical instruments to another patient is believed to be one method in which iatrogenic CJD occurs. Whilst surgical instruments are subjected to intensive cleaning procedures, it is unlikely that all prions are removed or deactivated and thus there is a risk that infections can occur during surgery. One potential method of minimising iatrogenic CJD is in the use of single-use surgical instruments, however this is likely to be associated with increased costs.

2 Data used and the scope of the model

The cost effectiveness analysis is based upon a mathematical model of a number of factors that could lead to CJD transmission. The model uses data on the delivery and volume of several types of operations; on surgical instrument use, reuse, and sterilization; on the likelihood of prions being transmitted by the intermediary of infective mass that adheres to instruments; the potential prevalence of CJD in the general population; and patient risk factors. The model is analyzed using discrete event simulation. Discrete event simulation allows patient populations and the contamination states of surgical instruments to evolve through time according to appropriate rules that account for random outcomes and system dynamics.

The literature search ¹ identified relatively few studies that could be directly used within our mathematical model. The submissions that were received by NICE provided few data relevant to populating the disease model. Data were more readily available for other relevant aspects of the model, such as cost data.

This section has therefore been sub-divided into two subsections. The first describes data where there was a great deal of uncertainty and which would be estimated from expert elicitation sessions, and the second describes data where fairly robust information was available. The second subsection was further sub-divided into those concerning operations, surgical instruments, patients and risks of infection.

This section also describes assumptions as to how the data were used in populating the model. Much of the structure of the model can be inferred by the types of data and the parameter estimates that are given in this section. The model is described further in Section 3 below.

Data estimated from elicitation sessions.

There was a good deal of uncertainty regarding a number of key decontamination and epidemiological parameters. It was decided that the best way to address these issues was to convene a meeting of experts and to attempt to elicit plausible distributions around these parameters. An overview of the principles of elicitation can be found in Garthwaite et al ² and O'Hagan et al. ³

CJDAS produced a list of experts in the field of epidemiology and decontamination of surgical instruments. The assessment group contacted these experts and chose the most suitable date to accommodate those experts who were willing to participate.

A group elicitation session was held independently for the epidemiologists and for the experts in the field of decontamination, with a separate meeting held for the issues relating to neuroendoscopy. The experts were brought together to a single meeting, and probability distributions were elicited to represent the beliefs of the group as a

¹ Patient Safety and reduction of risk of transmission of Creutzfeldt Jacob-Disease via interventional procedures. Systematic literature reviews. Lloyd Jones M, Stevenson M, Sutton A. 2006

² Garthwaite, P. H., Kadane, J. B. and O'Hagan, A. (2005). Statistical methods for eliciting probability distributions. *Journal of the American Statistical Association*, 100, 680-701.

³ O' Hagan, A., Buck, C. E., Daneshkhah, A., Eiser, J. E., Garthwaite, P. H., Jenkinson, D. J., Oakley, J. E. and Rakow, T. (2006). *Uncertain Judgements: Eliciting Experts' Probabilities*. John Wiley and Sons.

whole. The elicitation meetings were conducted by a facilitator, Dr J Oakley, (a statistician with experience in eliciting probability distributions).

The experts were first given a short presentation explaining the need for elicited probability distributions and how they would be used in the cost-effectiveness analysis. Relevant psychological biases in expert judgement (such as anchoring effects and overconfidence) were discussed. The experts then undertook a practice elicitation on an unrelated topic to familiarise themselves with the process of eliciting a probability distribution, and to identify and resolve any possible misconceptions or difficulties.

For each uncertain parameter, a complete probability distribution to describe the experts' uncertainty about that parameter was required. However, the experts were not asked to suggest a probability distribution directly. Instead, they were asked to provide a small number of summaries from their distribution; usually their median value and two further percentiles such as their 25th and 75th percentiles to describe their uncertainty about the parameter.

The facilitator would then choose a parametric probability distribution to fit these judgements as closely as possible, using the method of least squares. As an illustration, suppose the parameter of interest, θ , was a proportion and so known to lie between 0 and 1. Suppose the experts then state that their 25th, median (50th) and 75th percentiles of their distribution of θ are 0.2, 0.25 and 0.3 respectively, i.e., $P(\theta < 0.2) = 0.25$, $P(\theta < 0.25) = 0.5$ and $P(\theta < 0.3) = 0.75$. The facilitator would first choose an appropriate family of distributions, which in this case would be the Beta family, as Beta random variables are also constrained to lie between 0 and 1. Then writing $F(\theta; a, b)$ to denote the cumulative distribution function of a Beta(a,b) random variable, the facilitator now chooses values of a and b to minimise

$$\{0.25 - F(0.2; a, b)\}^2 + \{0.5 - F(0.25; a, b)\}^2 + \{0.75 - F(0.3; a, b)\}^2.$$

The facilitator then proposes the resulting Beta(a,b) distribution as a representation of the experts beliefs.

The above process of fitting a distribution to the expert's judgements using least squares can be done almost instantaneously, and so in the elicitation meetings the facilitator was able to immediately report the fitted distribution back to the experts. In particular, the experts were shown a plot of the density function and were fed back additional percentiles such as the 1st and 99th percentiles for comment. If the experts were not satisfied with the fitted distribution, then following discussion an alternative distribution would be proposed (with the experts possibly revising some of their initial judgements). The new distribution would also be reported to the experts, with the process repeating until the experts were satisfied that the fitted distribution was an acceptable description of their beliefs. In addition, a written summary of the meeting was sent to the experts at a later date, so that the experts had a further opportunity to review and comment on the chosen distributions.

Summaries of the elicited values for the key parameters, and the statistical distribution fitted to this are given in Tables 1 to 3. More detail is provided in Appendix 1 and Appendix 2. The elicited distributions for the epidemiological data were sent to additional experts in this area for comments. Based on these comments and on the

emergence of new evidence,^{4 5} a number of the previous elicited distributions have been changed. The key changes to the parameters are as follows.

- 1) The prevalence of patients who are m-v or v-v genotype that are incubating CJD has now been set to the distribution elicited for m-m genotype. Previously the experts believed that the prevalence in patients who are m-v or v-v genotype was lower than that for m-m, with a median for prevalence of 50% that of the m-m genotype, however this estimate has been revised in the light of new data.
- 2) The incubation period for patients infected at the central nervous system was assumed to be independent of genotype, and had a median duration of 2 years. This assumption has been revised, and the previous elicited distribution assumed to be applicable for patients that are m-m genotype only. The duration for the incubation periods for m-v and v-v genotypes were assumed to be 7 and 12 years respectively. The m-m distribution was log normal and the ratio of standard deviation to the median associated with this distribution was assumed applicable for the m-v and v-v genotypes.
- 3) The previous modelling work assumed that all patients infected with CJD would exhibit clinical symptoms if they lived long enough. This assumption has been revised to allow patients who have been infected to not exhibit clinical symptoms but remain in a carrier state, once the infectious period (that was estimated as though the patient had developed clinical symptoms) had been reached. This phenomenon was assumed to occur only in m-v and v-v patients. The proportion of patients assumed to be susceptible to clinical disease was assumed to be between 40-60% for m-v patients and 0-40% for v-v patients with both exhibiting a uniform distribution.

⁴ Bishop MT, Hart P, Aitchison L, Baybutt HN, Plinston C, Thomson V, Tuzi NL, Head MW, Ironside JW, Will RG, Manson JC. "Predicting susceptibility and incubation time of human-to-human transmission of vCJD." *Lancet Neurol.* 2006 May;5(5):393-8.

⁵ Ironside JW, Bishop MT, Connolly K, Hegazy D, Lowrie S, Le Grice M, Ritchie DL, McCardle LM, and Hilton DA. "Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study" *BMJ*, May 2006; 332: 1186 - 1188

Table 1: Summarised data on the elicited parameters regarding the decontamination of surgical instruments that are autoclaved

Parameter	Fitted Distribution	10 th Percentile	Median	90% Percentile
1) The log reduction in infectivity associated with autoclaving alone	Normal: mean 2.5, variance 0.551	1.55	2.50	3.45
2) The log reduction associated with subsequent autoclaving cycles. Expressed as a proportion of 1)	Beta (3.546, 18.969). mean 0.156, variance 0.006	0.07	0.15	0.26
3) Current detergent log reduction infection used in conjunction with autoclaving	Gamma (1.449, 2.255). mean 0.642, variance 0.285	0.12	0.50	1.35
4) Subsequent levels of reduction in infectivity due to current detergents. Expressed as a proportion of 3)	Beta (1.372, 1.522). mean 0.474, variance 0.064	0.13	0.50	0.83
5) Future detergent log reduction infection	Comment that a number of detergents with a log reduction of 6 are likely to be available in the relatively near future.			
6) Subsequent levels of reduction in infectivity due to future detergents. Expressed as a proportion of 5)	Beta (0.675, 10.212). mean 0.062, variance 0.005	0.003	0.05	0.16
7) The proportion of mass that has already been through one complete decontamination process that is washed off in the next washing cycle *	Beta (0.651, 70.451). mean 0.009, variance 0.0001	0.0004	0.005	0.02
8) The proportion of mass existing on instruments following previous decontamination cycles that will be transferred to a patient in an operation	Beta (0.750, 1.629). mean 0.315, variance 0.064	0.03	0.25	0.70

* For neuroendoscopes that can be autoclaved, the proportion of mass removed from the lumen has been set equal to the amount removed by subsequent cleaning cycles from autoclaved instruments. In all other aspects the neuroendoscope otherwise is treated as a standard instrument that can be autoclaved.

Table 2: Summarised data on the elicited parameters regarding the decontamination of neuroendoscopes that cannot be autoclaved

Parameter	Fitted Distribution	10 th Percentile	Median	90% Percentile
1) The percentage of mass within a lumen that is picked up by a neuroendoscopic accessory or scraped off when being passed down the lumen.	Beta(7.093, 20.457) Mean = 0.258, variance = 0.00672	0.16	0.25	0.37
2) The proportion of the mass from part 1) that will transfer to a patient and would present a risk of secondary infection if the mass was infectious. *	Beta(1.365, 2.895) Mean = 0.320, variance = 0.0416	0.07	0.29	0.61
3) The proportion of mass removed from the lumen and not transferred to the patient that remains adherent to the accessory. *	Beta(1.893, 2.953) Mean = 0.391, variance = 0.408	0.13	0.37	1.67
4) The proportion of mass picked up from the lumen and still adhering to the accessory that will be reapplied to the lumen on withdrawal. *	Beta(1.985, 9.142) Mean = 0.402, variance = 0.404	0.05	0.16	0.33
5) The proportion of residual mass on the lumen once the accessory had been passed down and withdrawn, that will be removed following the decontamination process. *	Beta(9.969, 1.587) Mean = 0.863, variance = 0.00941	0.73	0.88	0.97
6) The proportion of mass on the outside of the neuroendoscope that is transferred to the patient. [∇]	Beta(1.663, 13.107) Mean = 0.113, variance = 0.00640	0.03	0.10	0.22
7) The effect that the current cleaning process used with endoscopes that are not autoclaved has on the infectivity of prions	It was assumed that the current cleaning process had no effect on prions.			

* These proportions have also been assumed applicable to accessories that have been passed through a rigid neuroendoscope.

[∇] This proportion is also assumed to be applicable to rigid neuroendoscopes.

Table 3: Summarised data on the elicited parameters for epidemiological data

Parameter	Distribution	10 th Percentile	Median	90 th Percentile
1) The number of asymptomatic individuals, aged 16-39 years, m-m homozygote at codon 129, that are currently incubating vCJD per million in this group. [∇]	Beta(1.240, 2225.393)	84	400	1216
2) The ratio of the proportion of asymptomatic individuals, aged 0-15 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that are currently incubating vCJD.	Beta(0.883, 4.015)	0.02	0.15	0.41
3) The ratio of the proportion of asymptomatic individuals, aged 40-69 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that are currently incubating vCJD.	Beta(1.519, 5.396)	0.05	0.20	0.43
4) The ratio of the proportion of asymptomatic individuals, aged 70 years and above, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that are currently incubating vCJD.	Beta(2.718, 47.313)	0.02	0.05	0.09
5) The incubation period for an individual, of m-m genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery. (years)	Log normal, mean (on log scale): 0.693, s.d. (on log scale): 0.354	1 (2.5 th Percentile)	2	4 (97.5 th Percentile)
6) The incubation period for an individual, with m-m homozygote at codon 129, with secondary infection from tonsil to tonsil surgery. (years)	log normal, mean (on log scale): 2.076, s.d. (on log scale): 0.575	3 (5 th Percentile)	8	20 (95 th Percentile)
7) The incubation period for an individual, who is either m-v or v-v at codon 129, with secondary infection from tonsil to tonsil surgery. (years)	log normal, mean (on log scale): 2.993, s.d. (on log scale): 0.259	10 (5 th Percentile)	8	30 (95 th Percentile)
8) The population median proportion of the incubation period in which the patient is infectious at lymph tissue	Beta(166.212, 41.808)	0.76	0.80	0.83
9) The population median proportion of the incubation period in which the patient is infectious at the central nervous system.	Beta (0.750, 1.629).	0.17	0.20	0.23
Additional data elicited after the initial elicitation sessions				
10) The incubation period for an individual, of m-v genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery. (years)	log normal, mean (on log scale): 1.946, s.d. (on log scale): 0.349	4.48	7.00	10.95
11) The incubation period for an individual, of v-v genotype at codon 129, with secondary infection from central nervous system to central nervous system	log normal, mean (on log scale): 2.485,	7.53	12.00	19.10

surgery. (years)	s.d. (on log scale): 0.363			
12) The proportion of m-v patients that become infected but do not exhibit clinical symptoms, but remain as carriers	Uniform 0.4 – 0.6	0.42	0.50	0.58
13) The proportion of m-v patients that become infected but do not exhibit clinical symptoms, but remain as carriers	Uniform 0.0 – 0.4	0.04	0.20	0.36

[∇] For clarity reasons, the proportions determined from the Beta distribution have not been explicitly provided. Instead these have been multiplied by 1,000,000 to give the expected number of patients incubating CJD per million.

Data taken from the literature.

The cost effectiveness model was populated using published data regarding operations that might facilitate the transmission of CJD; surgical instruments; the rate at which surgical instruments might transfer tissue from one patient to another, even with cleansing; patient risk factors; and the consequences of negative outcomes.

Operations

Data regarding operations fall into three categories: the operations that were at most risk of potential transmission of CJD, the number of operations per year, and the population area considered.

The operations that were at most risk of potential transmission of CJD.

We contacted clinicians proposed by NICE to determine which operations, defined by Office of Population, Censuses and Surveys – Classification of Surgical Operations and Procedures – 4th Revision (OPCS-4) code, are likely to pose a risk of iatrogenic infection to patients. These were categorised into operations that were in the specialties of neurosurgery (intra-dural brain and spine), posterior eye (optic nerve and retina), anterior eye, maxillofacial, general surgery, general endoscopy, neuroendoscopy and anaesthetics. Appendix 3 provides further details about the specific operations that are assumed to be potential risks.

The number of operations undertaken per year.

In consultation with experts those operations considered at risk of contacting tissue with potentially high or medium titres of CJD infectivity are contained in Appendix 3. The numbers of these operations that are undertaken per year in England and Wales is given in Appendix 3. In calculating this number we have assumed, following advice from the Economics, Statistics and Operational Research division of the Department of Health, (ESOR) that the hospital episodes statistics (HES) data are increased by 15% to take into account operations undertaken by the private sector.

The population area considered.

We have restricted our analyses to a self-contained unit defined as a ‘modelling area’. This area is assumed to consist of one neurosurgical unit, one unit that undertakes posterior eye operations and a number of units that undertake the remaining operations. We have assumed that there are 27 modelling areas in England and Wales based on the number of neurosurgical centres, which is also the approximate number of posterior eye centres in England and Wales.

The total number of at-risk operations for England and Wales has been divided by 27 to estimate the number per modelling area. This is summarised in Table 4. In the model we have assumed that these operations are equally spaced throughout the year, and provide the deterministic inter-arrival time between operations. This corresponds to smoothly scheduled provision of operations through out the year. It is important because our model accounts for the time dynamics of incubation periods for CJD.

Table 4: The number of at-risk operations undertaken in a modelling area per annum

Specialty	Number of operations undertaken per year per modelling area	Inter-arrival Time for modelling area (days)
Brain	731	0.500
Spinal cord	77	4.754
Posterior Eye	1,353	0.270
ENT	3,650	0.138
Neuroendoscopy	25	14.610
Anterior Eye	13,931	0.026
Maxillo-Facial	7,313	0.050
General Surgery	14,633	0.025
General Endoscopy	34,766	0.011
Anaesthetics	2,350	0.138

Surgical Instruments

Data regarding surgical instruments fall into several categories: the number of sets for each specialty, supplementary instruments and accessories, instrument migration, natural wastage of instruments, the costs of surgical sets, and the amount of residual mass that remains on instrument sets.

The number of sets assumed for each specialty.

For each modelling area it was assumed that there were 12 sets of instruments for each specialty, which were used in rotation. For neuroendoscopy procedures it was assumed that there were 1 rigid neuroendoscopy set and 1 flexible neuroendoscopy set.

Supplementary instruments and accessories

Presently some instruments are available as individually packaged items. These are requested for particular operations and are then decontaminated and put back into the store and can subsequently be used with a different main instrument set. In our model we have assumed that there are 6 different types of supplementary instruments, each of which have 6 instruments that are used in rotation.

We have assumed that in an operation, for each type of supplementary instrument there is an independent 20% chance that an instrument is used. Thus for each operation the number of supplementaries used ranges from 0 (which has a probability of 0.8^6) to 6 (which has a probability of 0.2^6).

For neuroendoscopy procedures it was assumed that no supplementary instruments were used. We have assumed that one accessory is used in each operation, this is a simplification as sometimes more than 1 are used, but zero are used in assisted operations, where the neuroendoscope is used purely as a viewing aid.

Instrument migration

We have assumed that instrument migration is defined as an instrument moving from its native set at any point during the operation and the subsequent decontamination cycle. We have modelled separately instruments moving from one set to another and instruments from a set being substituted with similar supplementary instruments.

- 1) Instruments from one set becoming swapped with similar instruments in a separate set.

Following discussion with clinicians and some evidence provided by Scantrack in their submission, we have assumed that this occurs on 50% of all decontamination cycles. Where this does occur we have assumed that between 0% and 20% of the infectious mass of one set will be transferred to another set, with 0% - 20% of that set's mass transferred to the initial set. The values transferred are sampled independently for both sets.

- 2) Supplementary items becoming part of the basic set, with items from the set becoming supplementary items.

The model assumes that there is a 50% chance that a supplementary item is switched with a similar instrument from a set. When this happens, it is assumed that all infectious load residing on the supplementary is added to the set, and that a randomly sampled proportion (between 0 and 10%) of mass from the set is removed to reside on the 'new' supplementary item.

Natural wastage of instruments

Based on anecdotal evidence from a District General Hospital it was assumed that instruments are disposed of after, on average, 250 uses with this being sampled for each instrument after each operation. If the instrument disposed of is a supplementary instrument then all infectious mass is assumed to be destroyed. If the instrument was part of a set, it is assumed that a random proportion of the infective mass is destroyed. The percentage of mass disposed of per instrument for each specialty is given in Table 5 and is calculated based on the number of instruments in a set.

Table 5: The proportion of infective mass thrown away with a decommissioned instrument

Specialty	Instruments assumed to harvest potentially infectious mass during an operation	The possible proportion of infective mass thrown away with a decommissioned instrument *
Neurosurgery (assumed to represent both brain and spinal cord surgery)	18	0 – 12%
Posterior Eye	9	0 – 25%
ENT	23	0 – 11%
Neuroendoscopy	2	0 -100%
Anterior Eye	39	0 – 5%
Maxillofacial	64	0 – 3%
General Surgery	80	0 – 3%
General endoscopy	2	0 -100%
Anaesthetics	1	100%
Supplementary Instruments	1	100%

* The proportion of mass thrown away is randomly sampled between these ranges

The assumed costs of surgical sets.

Data were taken from the NHS Purchasing and Supply Agency (PASA) and used to estimate the expected costs of sets for each specialty. The instruments likely to be used in a typical operation were provided by clinicians.

For neurosurgery and posterior eye operations we have assumed that the subset of instruments that come into contact with high risk tissue is kept separately from those instruments used before the high-risk tissue is exposed. Very expensive items such as stereotactic neurosurgical frames, which do not come into contact with high-risk tissue have not been included within the model and are assumed to remain re-usable.

Summarised data is provided in Table 6. Since there are a number of suppliers only approximated prices are presented in this report.

Table 6: The estimated costs of surgical sets by specialty

Specialty	Approximate cost of a standard re-usable set. (£)
Neurosurgery (High risk tissue only)	3,500
Posterior Eye (High risk tissue only)	1,000
ENT	2,200*
Flexible Neuroendoscopes	9,300
Rigid Neuroendoscopes	397
Anterior Eye	2,200
Maxillofacial	2,600
General Surgery	3,000
General Endoscope	25,000
Anaesthetics (laryngoscope blade)	5
Endoscopy accessories (each)	100
Neuroendoscopy accessories (each)	200

*Single-use sets are already available for use in tonsillectomy and adenoidectomy procedures. These are assumed to cost £30 per set following data provided by a company submission.

Residual Mass remaining on instrument sets

We have used data provided by Professor Baxter and colleagues from the University of Edinburgh, which determined level of residual protein by acid stripping of instrument surfaces. In the calculation of infectivity the standard units are wet-tissue equivalent, which is assumed to be 5 times greater than the weight of protein.

From the Baxter data, the average wet tissue equivalent (the units in which infectious load are calculated) was 1.26 mg for general surgical instruments and 2.88 mg for instruments that had been used for tonsillectomies, although the range per instrument was wide. These data were broadly consistent with concurrent research undertaken at Bart's Hospital, the University of Southampton and the Centre for Applied Microbiology and Research. All the above research projects were supported and coordinated by the Department of Health Research and Development in CJD. Data from this research did not show any correlation between the complexity of an instrument and the residual mass. The standard deviation of mass on an instrument was estimated from the Baxter data. This was used for each specialty to estimate the expected

distribution of mass on a set and this was sampled for each specialty at the start of each simulation.

No empirical evidence is available on instruments used in neurosurgery or posterior eye operations and we have pessimistically assumed that these have the same residual mass as tonsillectomy instruments. The model has made a number of assumptions that have been pessimistic or optimistic. These are summarised in Appendix 4 with fuller descriptions given in the text.

It is unlikely that the residual mass on an instrument comes solely from the previous operation. As proposed by ESOR we have assumed a “steady state” approach to mass, with the residual mass remaining constant once the instrument has been used many times. From our elicitation exercise (see Appendix 1) the median value of residual mass that would be transferred to the patient was 25% with a median value of 0.5% of mass removed in subsequent decontamination cycles. Thus as a central estimate, approximately 25% of residual mass originates from the previous operation with the remaining 75% being from earlier operations.

If we assumed that 25% of the steady state mass on a set is from the previous operation then the average mass harvested per operation would be as given in Table 7.

Table 7: The estimated mass on a set following an operation and decontamination cycle by specialty

Specialty	Instruments assumed to harvest potentially infectious mass during an operation	Residual mass from one operation. Wet tissue equivalent (g)
Neurosurgery	18	0.0133
Posterior Eye	9	0.0067
ENT	23	0.0170
Anterior Eye	39	0.0273
Maxillofacial	64	0.0448
General Surgery	80	0.0560
General endoscopy	2	0.0014
Anaesthetics	1	0.0007
Each supplementary instruments used	1	0.0007

For neurosurgery and posterior eye operations we have assumed that the subset of instruments that come into contact with high risk tissue is kept separately from those instruments used before the high risk tissue is exposed.

For each specialty the number of instruments assumed to come into contact with potentially infectious tissue may be higher than that which occurs in everyday practice, as not all instruments within a set will be used, and some may not come into close contact with the patient. Thus the masses assumed are pessimistic.

The infectious titre of mass (in terms of ID50s- the dose that is required to infect 50% of people that receive it - per gram) by operation type is given below. Values have been taken from the ESOR report ⁶ and are endorsed by the Spongiform Encephalopathy Advisory Committee (SEAC). We have modified these slightly for

⁶ Assessing the risk of vCJD transmission via surgery. An interim review. Economic, Statistics and Operational Research. Department of Health 2005

our report by pessimistically assuming that all other tissue was at 4-log titre. Tonsillectomy tissue being put at the midpoint of the ESOR range but spleen was reduced to a titre of 4-log so that it could be modelled together with all general surgery. This data is summarised in Table 8.

Table 8: The estimated infectious titre of tissue in the ESOR model and the ScHARR model.

Risk	tissue	specialty	infectivity (log) - ESOR model	infectivity (log) – ScHARR model
high	CNS (excluding spinal cord and peripheral nerves), posterior eye	neurosurgery, neuro-endoscopy, ophthalmic surgery (posterior eye: retina, optic nerve)	8	8
	Spinal cord	neurosurgery	6	6
Medium	tonsils, spleen lymphoid tissue,	ENT and anaesthetics (tonsillectomy), general surgery (splenectomy)	4 - 5	4.5 (for tonsils), 4 for spleen
	lymphoid tissue, anterior eye, peripheral nerves	ophthalmic surgery (anterior eye), neurosurgery (peripheral nerves, CSF), general surgery, max/fax, endoscopy	3 - 4	4 (including spleen)
Low	all other tissue (e.g. GI tract, bladder etc)	general surgery, max/fax, endoscopy	3	4

Once instruments go through the decontamination cycle, some mass from previous operations is washed away, whilst any infectious mass will have its infectivity reduced by a combination of autoclaving and the detergents used within the decontamination process. The effectiveness of these measures has been elicited from decontamination experts, with a reduction in infectivity assumed in the first three cycles only (see Appendix 1). The median reduction expected in titre on a first decontamination cycle was 3 logs, although there is uncertainty around this value.

Assuming a 3-log reduction in infectivity due to autoclaving the average number of ID50s on a set immediately after an operation on an infectious person, after decontamination cycle has been calculated and is given in Table 9. This assumes that the instruments were free from prion contamination before the infectious operation.

Table 9: The average number of ID50s on a set following an operation on an infectious person and decontamination cycle

Specialty	Infectious Titre of tissue following a decontamination cycle (ID50s/g)	Residual mass from one operation. Wet tissue equivalent (g) (Table 7)	Average number of ID50s on a set following an operation on an infectious patient *
Brain	10^5	0.0133	1,330
Spinal Cord	10^2	0.0133	13
Posterior Eye	10^5	0.0067	670
ENT	$10^{1.5}$	0.0170	0.538
Anterior Eye	10^1	0.0273	0.273
Maxillofacial	10^1	0.0448	0.448
General Surgery	10^1	0.0560	0.560
Anaesthetics	$10^{1.5}$	0.0007	0.022
General endoscopy	10^1	0.0014	0.014
Supplementary Instrument (at 10^8) or neuroendoscopic accessory	10^5	0.0007	70
Supplementary Instrument (at 10^4) or general endoscope accessory	10^1	0.0007	0.007

* Calculated by multiplying the infectious titre by the expected number of grams of wet tissue.

It is seen that the number of ID50s on surgical instruments following an infectious operation is over 1 thousand for Neurosurgery. There is a clear distinction between those operation which contact tissue at a titre of 10^8 and those at a titre of $10^{4.5}$ and below.

A proportion of the infectious mass (median 25% from the elicitation exercise) is assumed to be transferred to subsequent patients undergoing an operation and can result in an infection. This is quantified in terms of an infectious load, defined as the product of infectivity and mass. It is noted that the infectious load is reduced by 1-log when the infection is transmitted via a peripheral site.

Assuming the elicited median values for the initial decontamination cycle and mass transferred to the patient, the number of ID50s received by a patient immediately after the set was used on an infectious patient is expected to be as given in Table 10. For peripheral sites, the number of ID50s transferred has been divided by 10, as this assumption has previously been endorsed by SEAC.

Table 10: The estimated number of ID50s transferred to a patient when a set used on an infectious patient is next re-used

Specialty	ID50s transferred to the next patient following an operation on an infectious person
Brain	333
Spinal Cord	3
Posterior Eye	168
ENT	0.013
Anterior Eye	0.002
Maxillofacial	0.011
General Surgery	0.014
Anaesthetics	0.006
Supplementary Instrument (at 10 ⁸) or neuroendoscopic accessory	17.5
Supplementary Instrument (at 10 ⁴) or general endoscope accessory	>0.001

When supplementary instruments are used, any infectious load on the instrument is added to the infectious load on the basic set, thus potentially increasing the risk of infection.

It is seen that there is a clear difference between the number of ID50s transferred from operations encountering tissue at 10⁸ infectivity and those encountering a maximum of 4.5 log.

We have assumed that there is no cross-contamination, i.e. that no high-risk tissue is transferred to instruments that do not come into contact with high-risk tissue from other instruments that do. This is an optimistic assumption. Assuming that the instrument would be used on a peripheral site, the infectious load would be reduced by 1-log. If the cross-contamination was the same amount as that residing on a supplementary instrument this would still represent 1.75 ID50s to be transferred to the next patient, using median assumptions, which equates to a risk of infection of 87.5%. The risk will diminish with successive patients as the tissue has undergone another decontamination cycle. As such the second patient the infected instrument was used on would have a risk of infection of 15.5. As such it may be prudent that instruments subject to contamination with high risk tissue should be disposed of.

On CJDAS advice we have not modelled the scenario where infection takes place without mass being transferred (contact theory). This may be an optimistic assumption.

The modelling of residual mass within endoscopes is more complicated, as even where single use accessories are used, there is still a chance of infecting the patient due to residual mass within the lumens of the endoscope. Flexible endoscopes cannot be autoclaved and will receive only detergent cleaning.

The likely mass transferred from a (neuro)endoscope lumen to a patient was estimated in an elicitation (see Appendix 1). There is a clear divide between rigid neuroendoscopes that can be autoclaved and flexible neuroendoscopes which cannot.

Using the data in Appendix 1, the expected number of ID50s that are transferred from the inside of a lumen to the following patient after an infectious endoscopy is given in Table 11.

Table 11: The estimated number of ID50s transferred to a patient when a neuroendoscope used on an infectious patient is next re-used

Source	Mass harvested in an operation (μg)	Infectivity of mass in lumen following detergent cleaning	Expected mass transferred to a patient (μg)	ID50s transferred to the next patient following an operation on an infectious person
Flexible Neuroendoscope	2.37	10^8	2.04	203
Rigid Neuroendoscope	0.48	10^4	0.08	0.008

In calculating the total risk posed from an endoscopy the total number of ID50s would be calculated by the summation of the individual ID50s contained on both the accessories and the lumen.

It is seen that on the first re-use of a flexible neuroendoscope following an operation on an infectious patient there is almost certainly an iatrogenic infection. However, due to the elicited distribution of residual mass removed from a flexible endoscope (see Appendix 1) then there are not a large number of subsequent infections from the first infectious patient.

The number of ID50s transferred following general endoscopy will be 1/1000 that of neuroendoscopy due to the relative infectious titre of the tissue. Thus the number of ID50s transferred immediately following an operation on an infectious patient where a flexible endoscope was used would be 0.203.

Patients

Data regarding patients fall into three categories: the age distribution of patients, the probability of infectious disease transmission to patients, and the likelihood of multiple operations (a risk factor for iatrogenic vCJD).

The age distribution of patients

The age at which patients undergo an operation will significantly affect the spread and impact of secondary CJD. As CJD is believed to be more prevalent within the relatively young (see Appendix 2), it is expected that operations in the young will encounter more patients incubating CJD. Where patients become infected, the greater the age the less the number of years lost will be, with an extreme scenario being that the patient has died through other causes before the end of the incubation period. The methodology for the derivation of the statistical distributions used to simulate the patient age for each specialty is given in Appendix 5. The maximum age of a patient undergoing an operation was assumed to be 95 years.

The initial prevalence and probability of disease transmission

There are two sources of randomness for disease transmission in the model. One is the initial prevalence of latent vCJD infection in patients that enter the model. [The guidelines for operations on patients with clinical CJD ensure that the instruments are disposed of, and thus we assumed these present no risk for subsequent infection via surgery] The other is associated with the probability of iatrogenic transmission to a patient that undergoes surgery as the model is simulated through time.

For the initial prevalence, the probability of an individual incubating CJD is expressed as a function of age classification (0-15 years, 16 – 39 years, 40 –74 years and 75 years and over) and genotype based on the elicitation exercise undertaken with a group of epidemiology experts (see Appendix 2).

As the simulation progresses, the number of patients infected, and the likelihood of their return to surgery will alter the probability of sampling an infectious patient.

It is assumed that individuals infected via secondary routes (e.g. surgery) become infectious only in the later stages of incubation, with median elicited estimates of the last 80% and 20% for tonsil tissue and central nervous system tissue respectively, based on the elicitation exercise undertaken with a group of epidemiological experts (see Appendix 2). The tonsil was used as a proxy for all peripheral tissue.

In the absence of data on when individuals infected via the primary (dietary) route become infectious, we have pessimistically assumed that all individuals currently incubating CJD are infectious (similarly to the assumptions made for a model on the risk of secondary CJD infections via blood transfusion that was undertaken for the Department of Health.)

<http://www.dnv.com/consulting/news/riskofinfectionfromvariantcjdinblood.asp>

As we have no data on when people incubating CJD at the start of the model from primary infection are likely to exhibit clinical symptoms, we have assumed that this does not occur within the time-frame of the model. Patients with clinical symptoms would not infect subsequent patients due to current guidance of discarding such

instruments, so this assumption may over-estimate the number of secondary cases. However were there a number of primary cases to become clinical, this may lead our experts to revise upwardly their central estimate on the prevalence of CJD in the community.

If a patient undergoing an operation is incubating CJD and is infectious at the time of the operation, then the instruments used can become contaminated with subsequent patients becoming infected.

Likelihood of multiple operations

A patient infected during surgery can infect further patients if he/she returns to have further operations whilst infectious. As such the probability of multiple surgeries can significantly affect the spread of CJD.

We have assumed that having had an operation in one specialty does not increase the risk of having an operation in a different specialty (e.g. having undergone neurosurgery does not increase the probability of undergoing posterior eye surgery). However it is plausible that having had neurosurgery, a patient may be expected to have more neurosurgical operations than someone who has no history of neurosurgery. In order to estimate the likely increased risk, HES data were extracted by a third-party.⁷ The data gave the number of operations per individual who had more than one operation, and whether this operation was undertaken within 6 months of the index operation. We have assumed that patients would not become infectious within 6 months, and that any operations undertaken within 6 months of the index operation would not pose a risk for secondary transmission.

The increased risk of returning to surgery for an individual with past history of operations of the same type compared with an individual of the same age, who had not had previous neurosurgery has been estimated as given in Table 12.

Table 12: The estimated rate of return to surgery, by specialty compared to people without a history of surgery in that specialty

.Specialty	Return to surgery ratio compared to a person without a history of an operation in the specialty
Brain	43
Spinal Cord	43
Posterior Eye	60
ENT	N/A
Neuroendoscopy	761
Anterior Eye	N/A
Maxillofacial	3
Anaesthetics	N/A
General Surgery	3
General endoscopy	4

Data was not obtained for ENT, Anterior Eye, and anaesthetics, however it is believed by our clinicians that these are low values (<5)

⁷ Northgate Information Solutions. <http://www.northgate-is.com/index/index.php>

The risk factors that are described above entail that the rate of return of patients to surgery be dynamic through time. The model was analysed with computer simulation, and computer logic was used to model the correlations that are implied by those dynamic risk factors. The methodology used to implement those correlations in patient return times to surgery is detailed in Appendix 6. This logic has been amended since the first report and has had a significant effect on the cost-effectiveness values.

Risks of Infection

The risks of infection for CJD are modelled in three steps: the probability of infection as a function of the infectious load, the consequences of a patient becoming infected, and reconciling those risks with the lack of observed iatrogenic vCJD cases.

Probability of infection based on infectious load

In the model we have assumed that there is a simple linear relationship between total ID50s received and infection probability (probability of infection = Number of ID50s/2), with 2 ID50s or more resulting in certain contraction. We have also assumed that there is no lower threshold value, below which disease transmission cannot occur. Both of these assumptions are pessimistic and can over-estimate the number of secondary infections.

The importance of instrument migration will be discussed. Where there are more than 2 ID50s on a set, the splitting of the set will lead to an increase in the number of expected secondary cases. Consider a scenario where a set contains 10 ID50s, if all of this mass is transferred to one patient, this patient would become infected. However was the set divided so that 5 people each received 2 ID50s, then 5 people will become infected. The overall increase due to instrument migration will be dependent on the efficacy of subsequent decontamination cycles and the proportion of infectious mass transferred to each subsequent patient.

At infectious loads below 2 ID50s splitting sets does not increase the number of expected secondary cases. For example, assuming that a set contains 1 ID50 the expected number of infections will be the same whether one person has an 50% risk, or whether 5 people each have a 10% risk. From previous data it is seen that the transfer of 2 ID50s or greater occurs in operations that encounter tissue at titres of 10^8 .

Our intention was to also simulate assuming an exponential approach with the risk of infection set to $(1 - 0.5^{\text{Number of ID50s}})$, however time constraints did not allow this. The rationale for the choice of the linear model first was that the SEAC had previously endorsed the linear approach. Any potential inaccuracy is likely to be constrained to circumstances where the infectious load is between 0.5 and 2 ID50s. Given that there is either a very high number of ID50s transferred to patients at central sites (neurosurgery, posterior eye, and neuroendoscopy) or very low number at peripheral sites (the remaining specialties analysed) the overall effect is likely to be small. The comparative risks of infection at selected numbers of ID50s are given in Table 13.

Table 13: The comparative risk of infection using linear and exponential risk formulae

Number of ID50s	Calculated risk using an exponential equation	Calculated risk using a linear equation
0.005	0%	0%
0.1	7%	5%
0.25	16%	13%
0.5	29%	25%
0.75	41%	38%
1	50%	50%
2	75%	100%
4	94%	100%
5	97%	100%
10	100%	100%

The consequences of a patient becoming infected

There is an incubation period before a patient who has been infected with CJD develops clinical symptoms. The average length of the incubation period is dependent on genotype and whether the infection was at a central site or at a peripheral site and has been elicited from our epidemiological experts (see Appendix 2). The incubation period is randomly sampled for each patient that becomes infected.

For patients who exhibit clinical CJD, it is assumed that their quality of life is reduced to zero for the remainder of their lives. The QALYs lost are then calculated assuming that the patient was expected to have a normal life expectancy if they had not contracted CJD. The QALYs accrued for each patient are discounted at 3.5% per annum.

Data was sought on the costs of treating a patient with clinical CJD. Few data were found and advice was taken from staff at the Department of Health. The following comments were received, and an assumption was made that the costs of treating a patient with CJD was £40,000.

- 1) An estimate based on a sample of 10 patients treated during 1994-1996 gave a range of £6,500 - £40,000 but probably missed some primary care inputs;
- 2) Looking at the average length of patient stay (105 days), using standard costs gave an indicative figure of £25,000 per patient;
- 3) The average time between diagnosis and need for in-patient treatment is 11 months. Taking into account other support received by patients and families suggested costs to the NHS in the range of £5,000 - £15,000.

Reconciling the risks of infection with the lack of observed cases of iatrogenic CJD.

Although as yet there have been no observed cases of iatrogenic CJD infection this does not mean that there is not a present risk. A number of factors, in isolation and in combination, could be consistent with the zero observed cases but could still create secondary CJD infections. These are

- 1) That people incubating CJD have only just reached their infectious period.

People incubating CJD are assumed to be infectious at central sites for approximately the last 20% of the incubation time (see Appendix 2). If the incubation period is suitably long, all operations to date on patients incubating CJD may have not presented a risk.

- 2) That the incubation period following infection at peripheral sites is lengthy.

The incubation period following infection at peripheral sites is expected to be lengthy. Patients may have been infected with CJD and are yet to exhibit symptoms.

- 3) That people incubating CJD have not reached an advanced enough age to undergo high-risk operations.

It is expected that the current prevalence of CJD incubation is greatest in the relatively young (15 – 39 year group). Operations on central sites are typically performed in more elderly groups. (Mean ages of 46 years and 60 years for neurosurgery and posterior eye operations respectively.) It may be that people incubating CJD since the primary outbreak have been too young to undergo an operation at a central site.

3 Modelling Methodology

Model Type and package employed.

The model is a discrete event stochastic simulation⁸ that accounts for patients, operations that are performed on them, the potential contamination of surgical instruments that may be infected with CJD, the effects of the sterilization of those instruments, and any potential secondary infections of additional patients due to prions on contaminated instruments. Each operation is simulated, as is the level of infectious mass on the instruments and the likelihood of infection and subsequent clinical onset (if appropriate).

The entities in the model include patients and surgical instruments. Attributes of patients include their age, which type of operation they need, whether they have undergone that operation within the simulation, and their health status with respect to CJD infection and clinical onset. Attributes of surgical instruments include whether they are in current use, are single-use instruments or not, the amount of residual mass from previous surgeries, and the amount of infectious agent, measured in ID50s, for CJD. Events of interest include the arrival of patients to surgery, the contamination of surgical instruments, the cleansing of surgical instruments, and the reuse of surgical instruments. Randomness comes from probabilistic outcomes including the number of operations per unit time for several types of procedures that can occur, the initial prevalence of CJD, and random secondary transmission events.

The main interventions that the model was designed to test includes (a) whether or not instrument sets remain together or migrate/mix with other sets as they are used, (b) whether or not single-use instrument sets are cost effective to use for several surgical procedures.

Time plays an important role in the model. The delay until the onset of clinical symptoms depends upon the time since infection. The age of the patients is modelled explicitly, and characteristics of disease transmission and mortality depend upon age. At the end of each simulated year, a proportion of the patients are assumed to die, in accordance with standard life tables, with the remainder aging 1 year. Newly borns are assumed not to be infected with CJD.

The nature of the interventions, the role of time, the importance of modelling stochastic events in small populations, led us to implement the model as a discrete event stochastic simulation, as opposed to a deterministic differential equation (also known as system dynamics, or compartmental) model. This choice, for example, allows us to model the contamination of none, one or a few instruments, whereas analogous compartmental models may lead to small fractions of a single instrument being contaminated, a mismatch with reality that we preferred to avoid.

At a high level, there are two sources of uncertainty in the model. The first source of uncertainty is regarding the parameter values, such as those parameters whose distributions were estimated as part of the expert judgment elicitations. The second source of randomness comes from the random numbers of patients and chance

⁸ Averill M. Law and W. David Kelton, 2000, Simulation Modeling & Analysis, 3rd edition, McGraw-Hill, Inc. New York.

behaviour of infection transmission events. The second source of randomness will cause different outcomes to emerge from the model even if the same parameters are input. Both sources of randomness are appropriate in this application.

This section describes how several specific scenarios were tested in “Modelling approach”. Technical details regarding the running of individual stochastic simulation runs, along with a justification in terms of model duration, are given in “Warm Up Period” and “The Time Horizon”. The ensuing section describes the iterative modelling approach that was used to reduce the time that was needed to compute the simulation results, while still allowing for a workable and useful output for the analysis. Then the policy options that were assessed are described in more detail. Finally, a description of the cost effectiveness acceptability curves (CEAC) are described for the various measures. Those curves describe the probability that an intervention is cost effective as a function of the acceptable cost per QALY level.

The model has been implemented in the commercial simulation package Simul8 2005 Professional edition. (©Simul8 Corporation).

Modelling approach.

Due to the complexity of the modelling an iterative approach to the problem was undertaken, with preliminary results presented to the CJDAS that were based on selected scenarios. These scenarios usually took the form of either median values (the most likely parameters) or a more pessimistic scenario where the prevalence of CJD in the 16-39 group was set higher than expected (at the 90th percentile) and the effectiveness of decontamination lower than expected (at the 10th percentile) with all other parameter values at the median.

These scenarios were discussed within the CJDAS. Where the data strongly supported a conclusion, then the decision that was implied by that conclusion was taken. Throughout the initial months of modelling the assumptions within the model were appraised and adjusted as necessary.

Once the appropriate modelling question was arrived at full probabilistic sensitivity analyses were conducted allowing an insight into the mean and ranges of cost per QALY values.

A diagram of the conceptual model is shown in Figure 1.

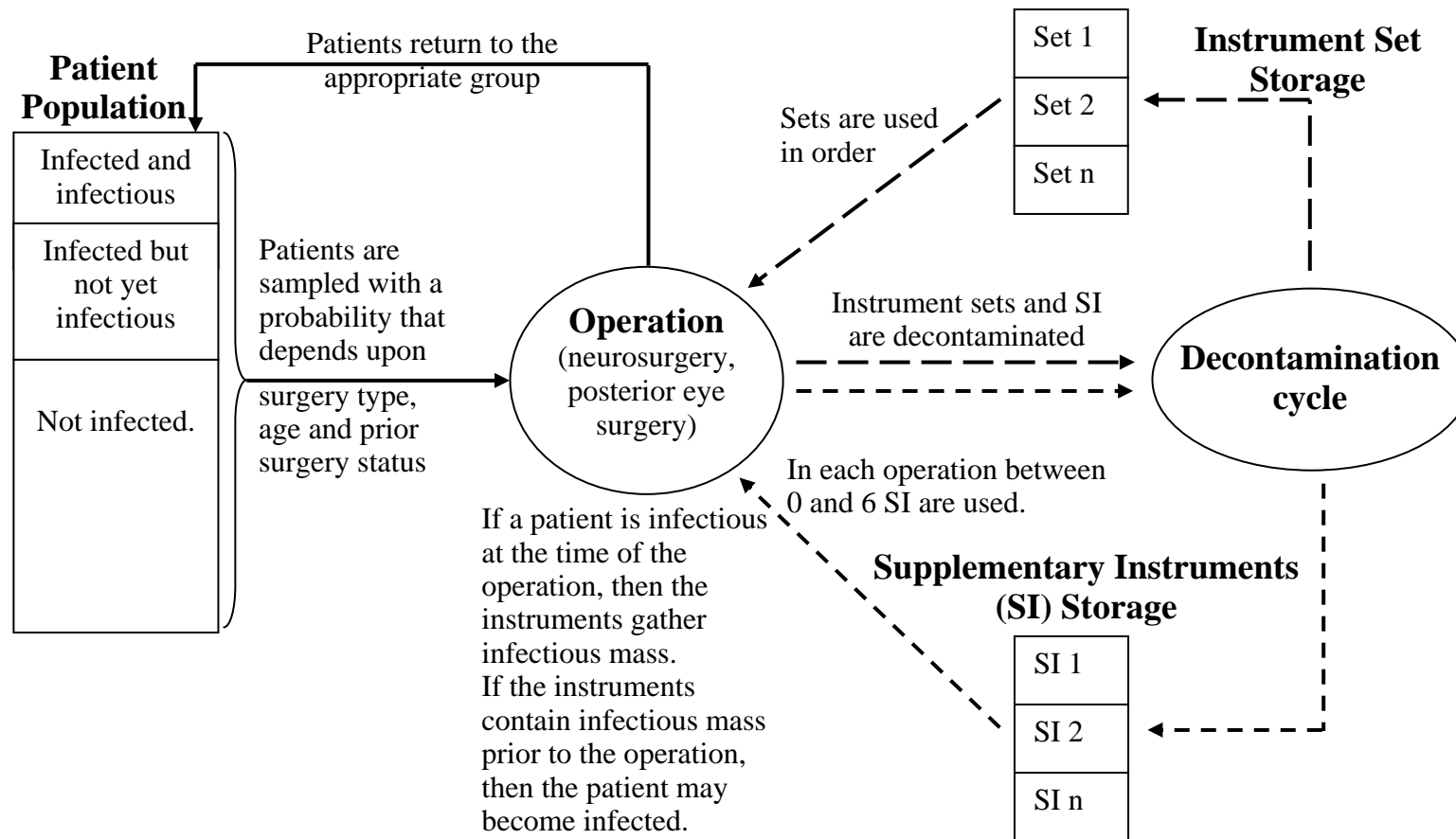


Figure 1. Flows of patients, instrument sets, and supplementary instruments (SI), with potential for iatrogenic transmission during an operation. The decontamination cycle removes mass from the instruments and reduces the infectious titre where applicable. During the operation, in the decontamination process, and in the instrument storing process, instruments may migrate between sets. Additionally SIs cannot always be identified amongst similar items from the main set, and migration of SI and set items can occur.

Duration of Simulated Time in Simulation Runs.

Each simulation run consisted of an initial “warm up” period, during which no statistics were collected, and a “data collection” period, during which statistics were collected in order to estimate the costs and benefits of a given intervention.

It is good practice within simulation models to not start the model ‘cold’, with for example the assumption of no infectious mass currently on instruments. In order to start the simulation in a typical state, we used a warm-up period for the model of 2 years. During this time period it is assumed that the population incubating CJD have all been infectious and that instrument migration has been occurring. The results collection period begins after this when it is assumed that any policy changes that are to be evaluated are made.

Throughout the warm-up period we have assumed that brain, spinal cord and posterior eye sets have been segregated into those instruments that contact high-risk tissue and those that do not. This is an optimistic assumption.

Given that the average incubation period for infection at a central site, where the risks are greatest, is 2 years (see Appendix 2) and that to date there have been no observed secondary infections, we have assumed that modelling historical time periods greater than 2 years ago would not be necessary.

The data collection period for simulation runs of the model was 5 years. This duration was chosen as the CJDAS believe that an effective prion decontamination intervention is likely to become available for use in the NHS within 5 years. Analyses were undertaken assuming an additional 5-log reduction in infectivity due to the intervention compared with current decontamination cycles. A 5-log reduction was chosen as this was the lower ranges of efficacy data in reports of new interventions submitted confidentially to NICE. Such interventions effectively reduced the number of iatrogenic CJD infections to zero, and it was assumed that analysis beyond 5 years was not necessary. This represented a crude reduction of 95% in computational time.

Simplifying the model to decrease computational time.

The full model that has been described above was computationally very expensive. In the model-building process, a number of comparative scenarios were analysed, and where there was little difference in the results, but significant improvements in the computational time required, the simplified model was used. This led to the exclusion of sites where infectious titre is relatively low.

For each modelling area there are approximately 2,200 operations per year that encounter tissue that could have an infectious titre of between 10^6 and 10^8 ID₅₀s. There are approximately 76,600 operations that could encounter tissue between 10^4 and $10^{4.5}$ ID₅₀s. Initial model runs showed that even under pessimistic assumptions the number of iatrogenic cases in the latter group was small, both absolutely (an average of marginally over 1 case per year) and relatively compared with the 21 iatrogenic cases per annum predicted for high risk tissue. Given the high cost of introducing single use instruments for these operations, such a policy would not be

cost-effective, with cost per QALY values greater than £2 million. It is also noted that we have pessimistically assumed that low-risk tissue have a titre of 4-log.

Additional cost-effectiveness analyses were undertaken for tonsillectomies and adenoidectomies, where single use instruments are available and relatively inexpensive. The cost per QALY of single use instruments was seen to be over £500,000 using median scenarios and over £50,000 assuming the upper 10th percentile for prevalence and lower 10th percentile for decontamination effect.

Given these results, the model was simplified to contain only those operations that could encounter tissue of 10⁶ or greater ID50s, namely neurosurgery, posterior eye and neuroendoscopy. This represents a crude reduction in computational time of 97%.

The policy options evaluated.

Our analyses focussed on three broad policy options regarding single-use instruments. The analysis also assessed the effects being able to control instrument migration completely, as compared with what is believed to be current levels of instrument migration. For all analyses we have assumed that single use and re-usable instruments have the same complication rates, with measures in place to ensure that the quality of single-use instruments remains high. Sensitivity analyses have shown that the impact of small average QALY losses per operation due to inferior single use instruments can result in a greater number of QALYs lost than through iatrogenic CJD, as such a procurement procedure to ensure the quality of single-use instruments will be necessary were single-use instruments recommended.

We have assumed that the cost of autoclaving a re-usable set is approximately the same as the safe disposal of single-use set. As such, neither of these considerations has been modelled.

The three broad policy options for the use of single-use instruments are:

a) Continue with re-usable instruments for all patients

This approach would assume that re-usable instruments are used in high-risk specialties. Preliminary results from such runs show that relatively large numbers of iatrogenic cases in neurosurgery and posterior eye is likely once an operation has been performed on an infectious person in that specialty. Without other interventions this could produce a self-sustaining epidemic.

b) Use single-use instruments for patients with a previous history of high risk surgery and re-usable instruments for all remaining patients

The rationale behind using a targeted approach to patients with a history of high-risk surgery is that these patients may have a higher expected prevalence of CJD since they have been subjected to operations with a risk of secondary infection.

For computational simplicity the results for option 2 have been calculated assuming that the instruments used in brain surgery on patients with a history of brain surgery

would be disposed of. Similarly, instruments that are used in posterior eye operations on patients with a history of previous posterior eye operations would be disposed of. The logical extension to this would be to dispose of all instruments used in high-risk operations on patients with a history of high-risk operations. Whilst this has not been explicitly modelled it is unlikely to alter the results significantly, since we have assumed no increased risks of brain surgery following a posterior eye operation and vice versa, and the numbers of patients who undergo both brain surgery and posterior eye surgery is likely to be small. This approach would stop anyone infected during surgery being able to infect subsequent patients if they returned to surgery. This would limit the number of CJD cases and, assuming that no other methods of CJD contraction (such as blood transfusion) were possible, would prevent a self-sustaining epidemic. However there could still be large number of secondary infections from patients undergoing a first operation whilst incubating CJD. These infections would be episodic and consist of a cluster of secondary infections associated with an infectious index case, with the number of cases declining as the infectious load diminishes.

c) The introduction of single use instruments for all patients in high-risk operations.

This approach would mean that there would be no secondary cases due to surgery, although it would result in large financial costs.

Incremental analyses have been undertaken, initially comparing the cost-effectiveness of the targeted approach with maintaining re-usable instruments. The second analysis estimates the incremental cost-effectiveness of moving from a targeted approach to one of single-use instruments for all operations.

These analyses have been performed twice, one where instrument migration is maintained at the estimated current level, and once where instrument migration has been assumed to be prohibited. These could be achieved by the use of tracking systems to ensure that all sets in high-risk specialties are kept together, and by abolishing the use of supplementaries.

The cost-effectiveness of neuroendoscopes and associated accessories has been undertaken in isolation from the main analyses. This is due to the need to evaluate the cost-effectiveness when both, either or none of the neuroendoscope or the accessory is made single use. This is optimistic as any secondary infections following neurosurgery or posterior eye operations will not increase the prevalence of CJD in patients undergoing neuroendoscopy, and vice versa.

Methodology for producing results

One thousand (1,000) sets of parameter values were sampled from the appropriate distributions for the following parameters (see Appendix 1 and Appendix 2 for details of the distributions used).

1. The infectivity reduction associated with autoclaving
2. The infectivity reduction associated with current detergents
3. The prevalence of CJD by age group

4. The proportion of mass removed on decontamination cycles after the first
5. The proportion of mass transferred to the patient
6. The incubation period following secondary infection via a central site
7. The proportion of the incubation period at which central sites infectious
8. The mass contained per set per specialty
9. The mass contained in the lumen of neuroendoscopes
10. The mass contained on the outside of neuroendoscopes
11. The percentage of mass within a lumen that is picked up by an neuroendoscopic accessory and transferred to a patient
12. The proportion of residual mass on the lumen once the accessory had been passed down and withdrawn, that will be removed following the decontamination process.
13. The proportion of mass on the outside of the neuroendoscope that is transferred to the patient.

For each of the 1,000 input parameter sets, we ran 50 simulation replications with different random numbers, in order to account for the variability in the actual outcomes, and to estimate the mean costs and benefits for each individual set of input parameters. Thus 50*1000 replications were undertaken looking at both parameter and stochastic uncertainty.

For each specialty analysed the summary of the results are presented in terms of

The mean costs associated with the 1,000 parameter settings
The mean QALYs associated with the 1,000 parameter settings

This methodology is summarised in the following algorithm.

1. For $i = 1, 2, \dots, 1000$ parameter settings
 - a. Sample input parameter Θ_i (set of all parameter uncertainties, from elicited distributions of unknown parameters).
 - b. For $j=1,2, \dots 50$ simulated outcomes for each parameter setting
Run the simul8 model to get cost_{ij} and QALY_{ij}
 - c. Compute $\text{Cost } i = \text{average over the 50 outputs for the } i\text{th parameter setting}$
 - d. Compute $\text{QALY } i = \text{average over the 50 outputs for the } i\text{th parameter setting}$
2. Compute the overall sample mean costs and sample mean QALYs

We also present cost-effectiveness acceptability curves (CEACs). CEACs are used graphically to depict uncertainty concerning the cost-effectiveness of decisions involving alternative interventions. They represent the probability that a given intervention is cost-effective (y axis) over a range of cost-effectiveness thresholds that

may be set by the policy maker (x axis). The CEACs we present will be based on the 1000 (Cost i , QALY i) pairs that correspond to input parameter uncertainty.

For neuroendoscopy only 500 parameter sets were run.

4 Results

The results are presented in terms of one modelling area with the assumption that these are applicable to all other modelling areas. At present there are few single use instruments available for neurosurgery and posterior eye operations and thus single use instruments are assumed to cost the same as re-usable instruments. There has been a tender for single-use neurosurgical and posterior eye instruments recently issued by PASA and it is expected that the costs of these instruments will fall.

The results have been split into two sections, those produced when instrument migration has been prohibited, and those where instrument migration has been assumed to continue at the currently estimated rate.

The results that are presented in Table 14 and Table 15 assume that in brain, posterior eye and spinal cord surgery that current re-usable items are thrown away after one use and that instrument migration has been prohibited.

As can be seen from the reference ranges there is a great deal of uncertainty in the cost-effectiveness of single use instruments and this include scenarios with no QALY gains associated with the introduction of single use instruments.

Additional information is provided in Figures 2 to 4, which depict the CEAC for each speciality when instrument migration has been prohibited. Figures 5 to 7 provide this information when it is assumed instrument migration continues at the currently estimated rate.

Note that the data for an individual modelling area are very skewed and the median individual cost-effectiveness ratio does not equate to the mean cost per QALY. This is because the bulk of scenarios produce small QALY gains where the intervention does not appear to be cost-effective. However there are a small number of 'catastrophic' scenarios with a large number of iatrogenic cases which are associated a very large QALY loss. These latter scenarios heavily influence the calculation of the mean cost per QALY. We also provide data on the probability that the cost per QALY is below £30,000, which is often assumed to be a threshold of cost-effectiveness in the UK.⁹

Assuming a £30,000 cost per QALY threshold, the level of money that can be spent cost-effectively to prohibit instrument migration can be calculated. Assuming re-usable instruments are maintained, an additional 198 and 364 QALYs were lost per geographical area over 5 years in brain and posterior eye surgery respectively where instrument migration was allowed to continue. These would translate into maximum expenditure over a 5-year period of £5.9m and £10.9m per brain unit and posterior eye unit respectively to prohibit instrument migration whilst still remaining cost-effective. The benefits of maintaining sets may also have benefits further reaching than purely in reducing the number of secondary CJD infections.

⁹ National Institute of Clinical Excellence. Guide to the Methods of Technology Appraisal. NICE, 2004.

Table 14: The mean cost per QALY values per specialty assuming re-usable instruments are disposed of following one use and that instrument migration is prohibited.

Specialty	Comparison	Mean Cost Per QALY (£)	95% Reference Range for Cost per QALY (£) (2.5% - 97.5%)
<i>Targeted Approach</i>			
Brain surgery (High risk tissue only)	Single use instruments targeted at those patients which have had prior brain surgery compared with re-useable instruments.	99,481	14,013 - infinity
Posterior Eye (High risk tissue only)	Single use instruments targeted at those patients which have had prior brain surgery compared with re-useable instruments.	45,181	2,377 - infinity
Spinal Cord surgery (High risk tissue only)	Single use instruments targeted at those patients which have had prior brain surgery compared with re-useable instruments.	392,376	46,542 - infinity
<i>Incremental Single-Use for all</i>			
Brain surgery (High risk tissue only)	Single use for all compared with single use for patients with previous posterior eye surgery	157,831	22,599 - infinity
Posterior Eye (High risk tissue only)	Single use for all compared with single use for patients with previous posterior eye surgery	58,625	6,961 - infinity
Spinal Cord surgery (High risk tissue only)	Single use for all compared with single use for patients with previous posterior eye surgery	6.38m	817,455 - infinity

The 95% reference range for each specialty as taken from the CEAC and is derived from the 2.5% and the 97.5% points

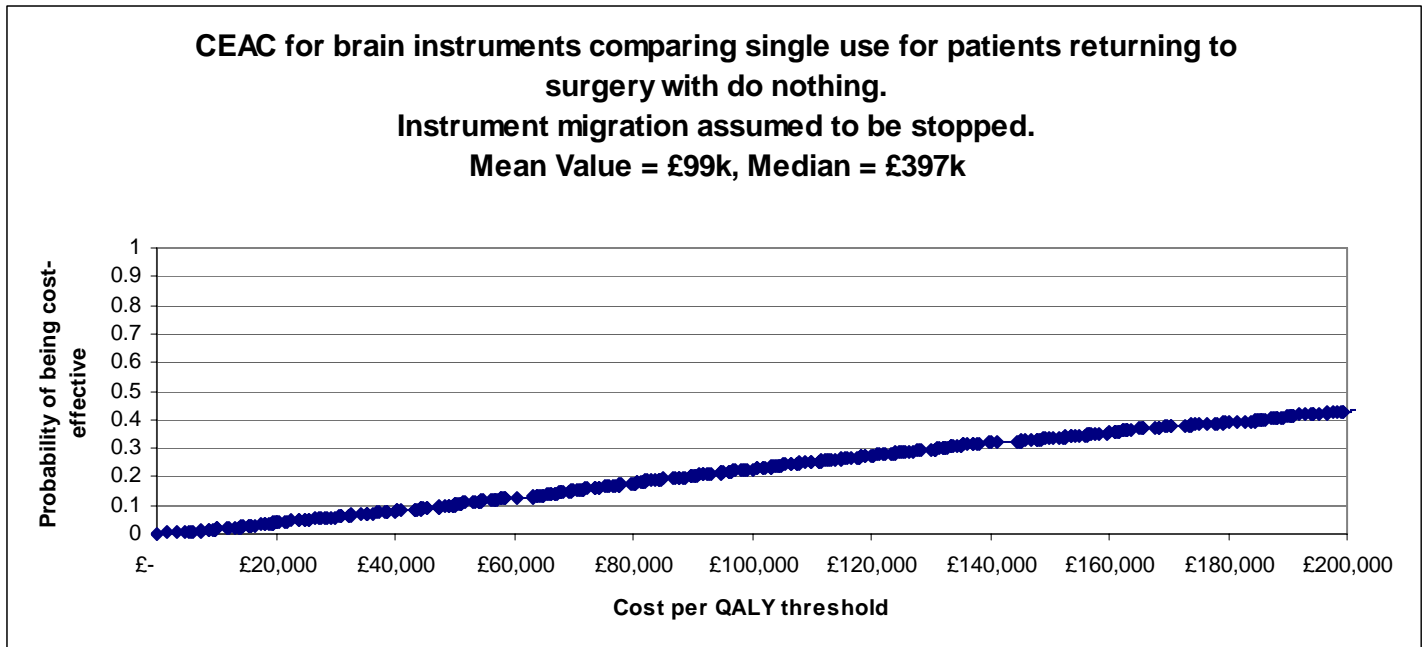
Table 15: The mean cost per QALY values per specialty assuming re-usable instruments are disposed of following one use and that instrument migration continues at the currently estimated rate.

Specialty	Comparison	Mean Cost Per QALY (£)	95% Reference Range for Cost per QALY (£) (2.5% - 97.5%)
<i>Targeted Approach</i>			
Brain surgery (High risk tissue only)	Single use instruments targeted at those patients which have had prior brain surgery compared with re-useable instruments.	18,666	351 - infinity
Posterior Eye (High risk tissue only)	Single use instruments targeted at those patients which have had prior brain surgery compared with re-useable instruments.	3,819	Dominating * - infinity
Spinal Cord surgery (High risk tissue only)	Single use instruments targeted at those patients which have had prior brain surgery compared with re-useable instruments.	252,133	39,285 - infinity
<i>Incremental Single-Use for all</i>			
Brain surgery (High risk tissue only)	Single use for all compared with single use for patients with previous posterior eye surgery	46,739	3,493 - infinity
Posterior Eye (High risk tissue only)	Single use for all compared with single use for patients with previous posterior eye surgery	16,399	Dominating * - infinity
Spinal Cord surgery (High risk tissue only)	Single use for all compared with single use for patients with previous posterior eye surgery	4.82m	551,381 - infinity

The 95% reference range for each specialty as taken from the CEAC and is derived from the 2.5% and the 97.5% points

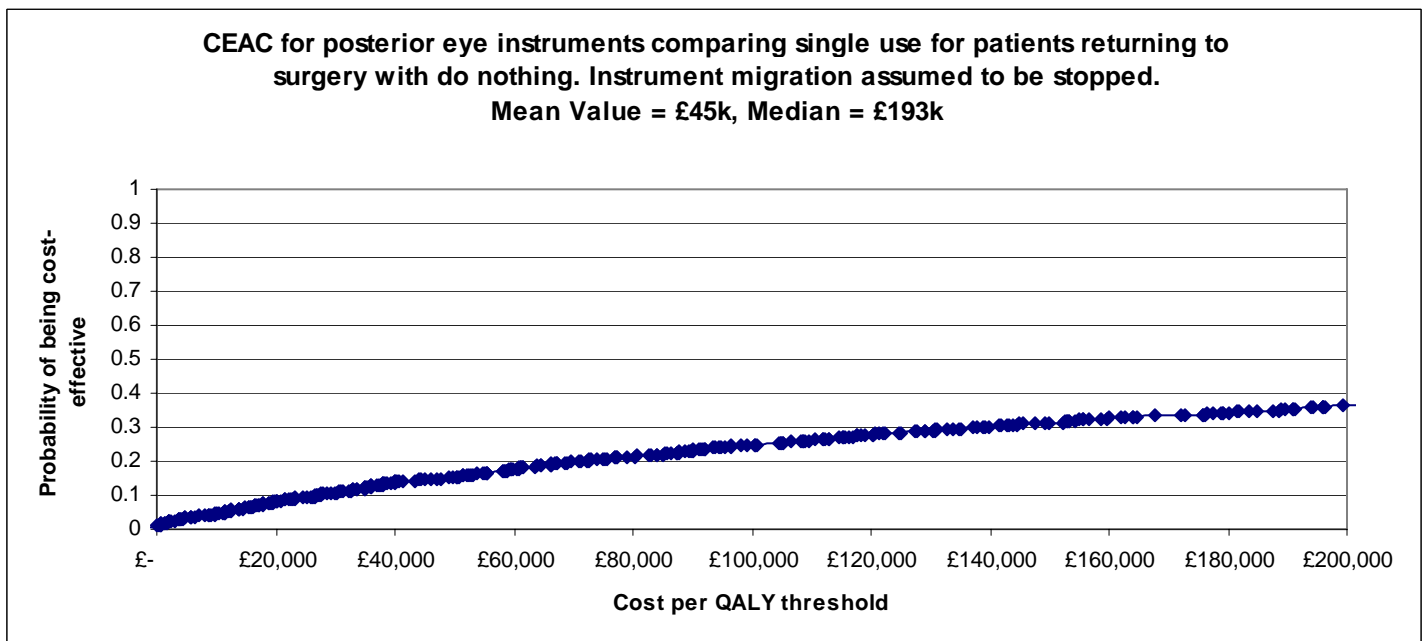
* Dominating means that the intervention is highly cost-effective. It is associated with a negative cost per QALY, since costs are saved and QALYs are gained.

Figure 2: The CEAC for brain surgery assuming that re-usable instruments are thrown away following one use and that instrument migration is prohibited



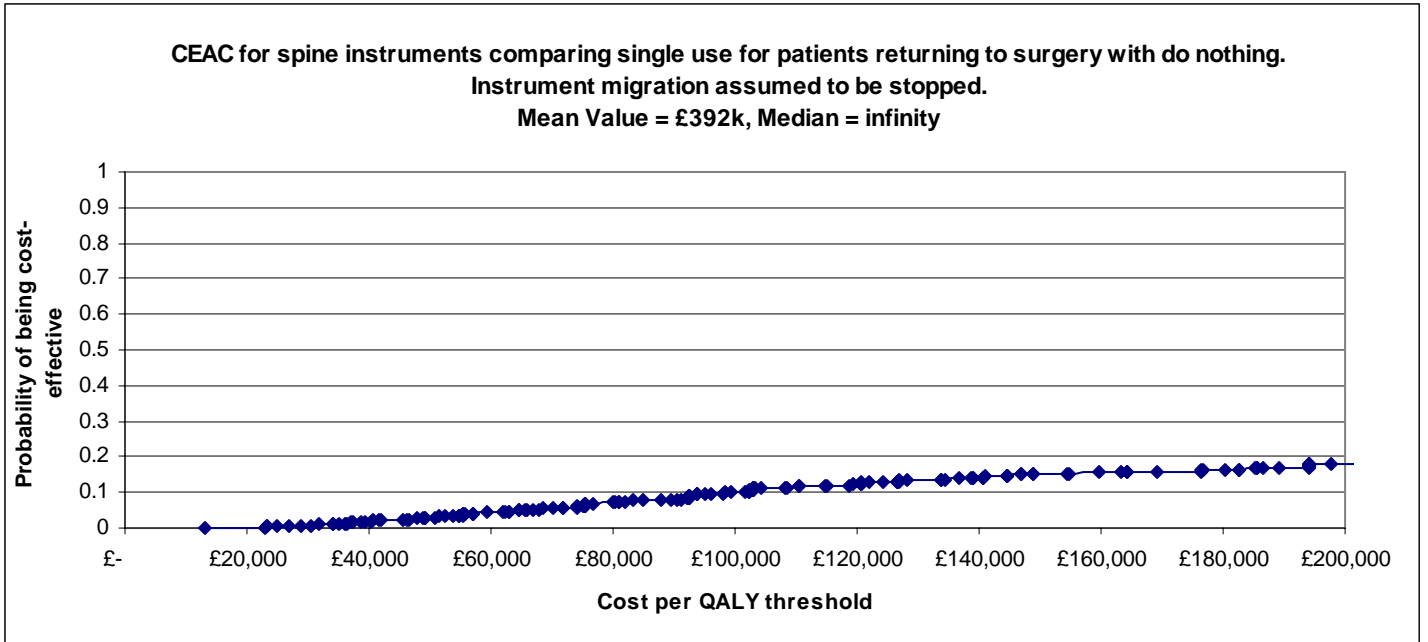
Proportion of times cost per QALY is below £30,000 = 6%

Figure 3: The CEAC for posterior eye surgery assuming that re-usable instruments are thrown away following one use and that instrument migration is prohibited



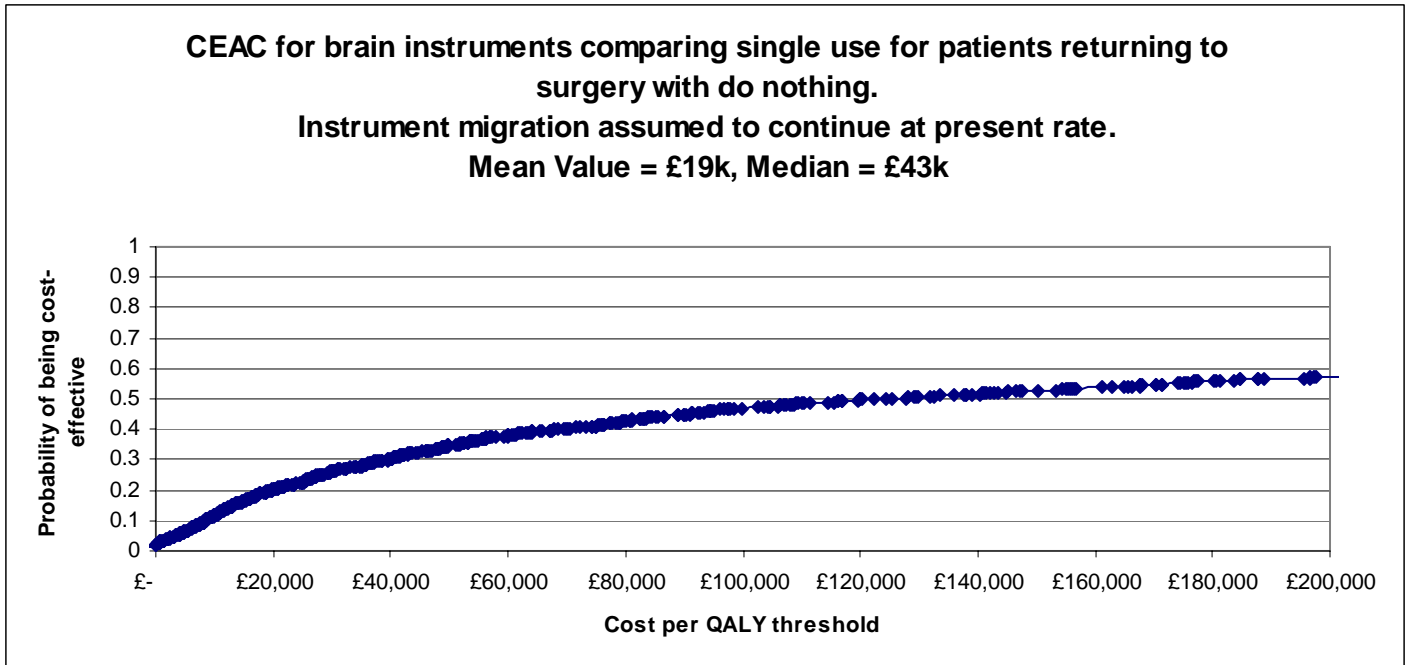
Proportion of times cost per QALY is below £30,000 = 11%

Figure 4: The CEAC for spinal cord surgery assuming that re-usable instruments are thrown away following one use and that instrument migration is prohibited



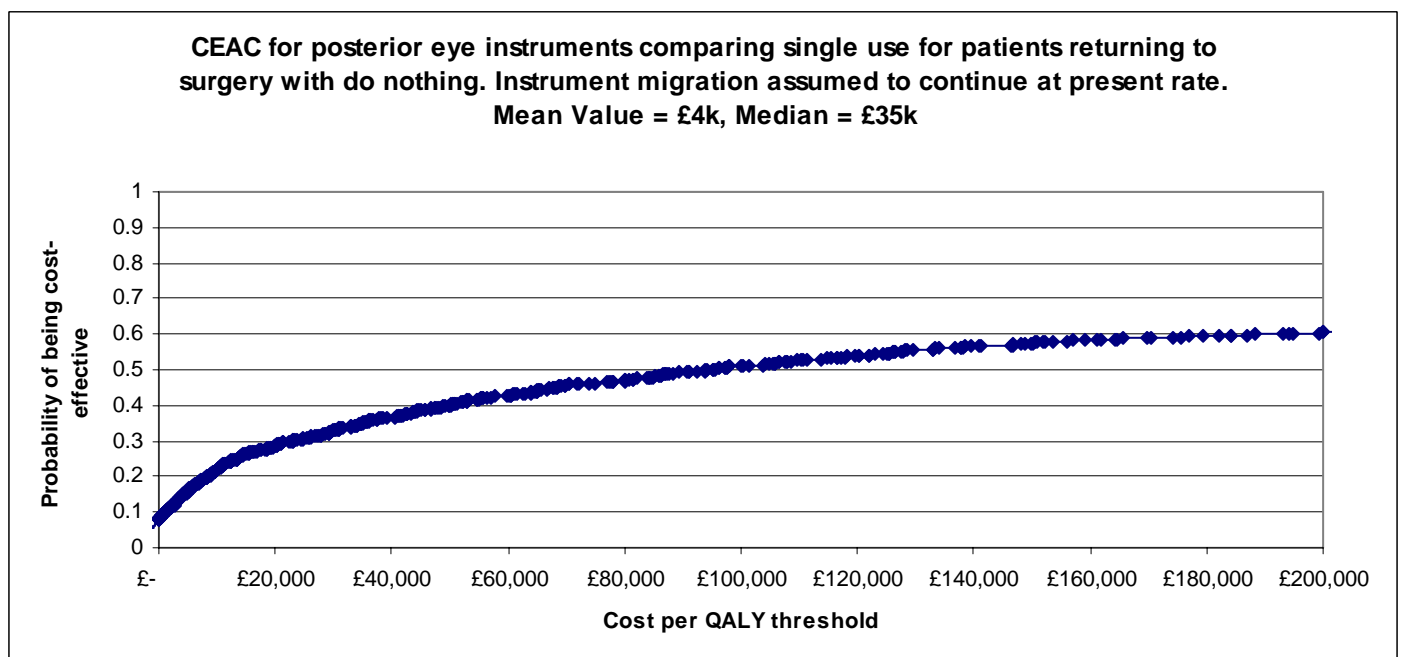
Proportion of times cost per QALY is below £30,000 = 1%

Figure 5: The CEAC for brain surgery assuming that re-usable instruments are thrown away following one use and that instrument migration continues at the currently estimated rate.



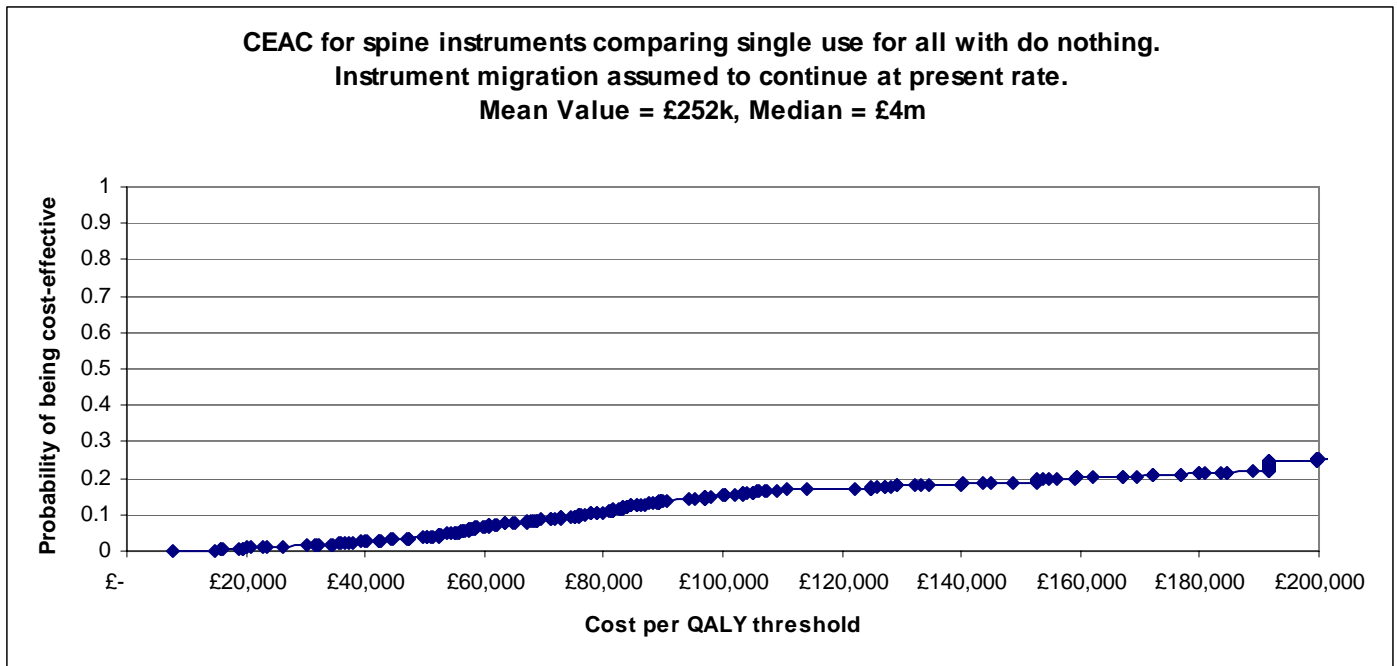
Proportion of times cost per QALY is below £30,000 = 26%

Figure 6: The CEAC for posterior eye surgery assuming that re-usable instruments are thrown away following one use and that instrument migration continues at the currently estimated rate.



Proportion of times cost per QALY is below £30,000 = 33%

Figure 7: The CEAC for spinal cord surgery assuming that re-usable instruments are thrown away following one use and that instrument migration continues at the currently estimated rate.



Proportion of times cost per QALY is below £30,000 = 1%

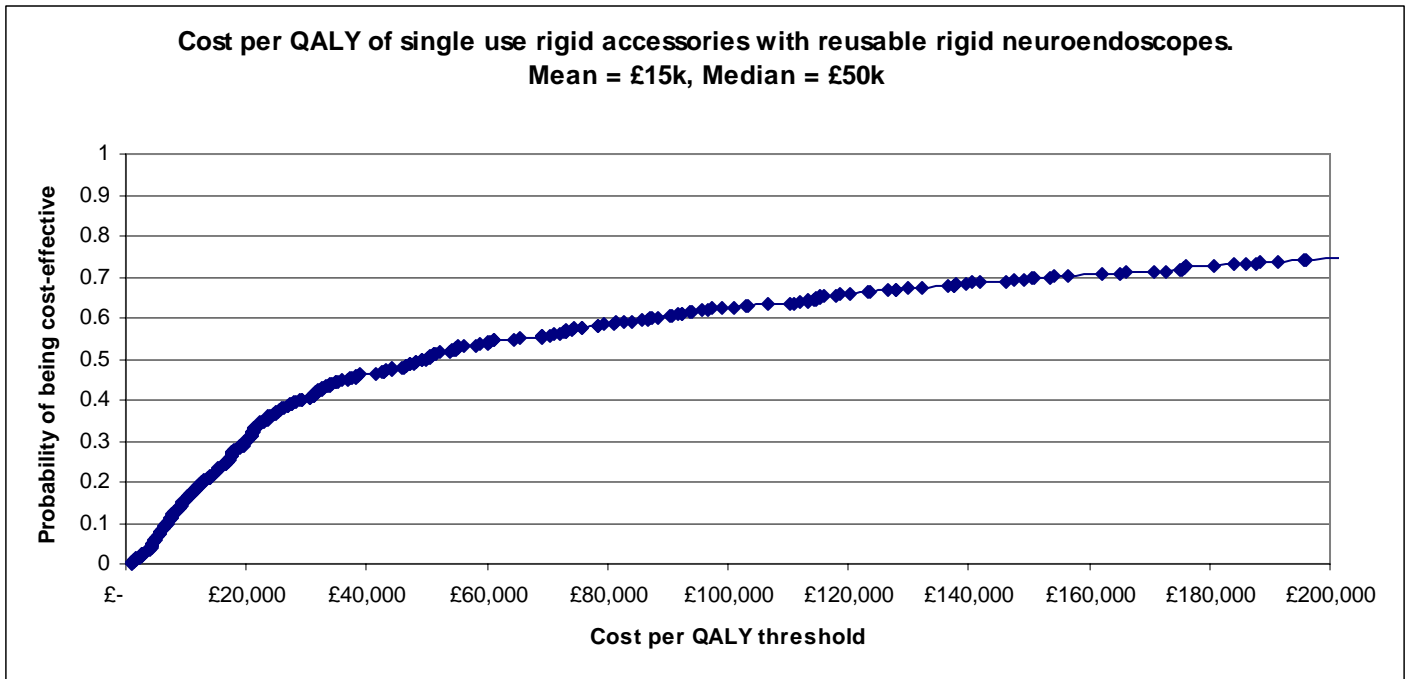
Table 16 details the cost per QALY values for neuroendoscopy. This has been modelled without instrument migration and incremental analyses single use accessories and then the introduction of single-use neuroendoscopes. Separate analyses have been undertaken for rigid and flexible neuroendoscopes as these differ both in terms of price and ability to withstand autoclaving. The CEACs for rigid neuroendoscopes are provided in Figures 8 and 9, with the CEACs for flexible endoscopes depicted in Figures 10 and 11.

Table 16: The mean cost per QALY values for neuroendoscopy.

Specialty	Comparison	Mean Cost Per QALY (£)	95% Reference Range for Cost per QALY (£) (2.5% - 97.5%)
<i>Rigid Neuroendoscopes</i>			
Single use accessories	Single use accessories compared with re-useable accessories assuming a re-usable neuroendoscope.	15,488	2,805 - infinity
Single use neuroendoscope	Single use neuroendoscope compared with re-useable neuroendoscope assuming single use accessories.	126,249	14,903 - infinity
<i>Flexible Neuroendoscopes</i>			
Single use accessories	Single use accessories compared with re-useable accessories assuming a re-usable neuroendoscope.	21,609	3,128 - infinity
Single use neuroendoscope	Single use neuroendoscope compared with re-useable neuroendoscope assuming single use accessories.	1.13m	281,858 - infinity

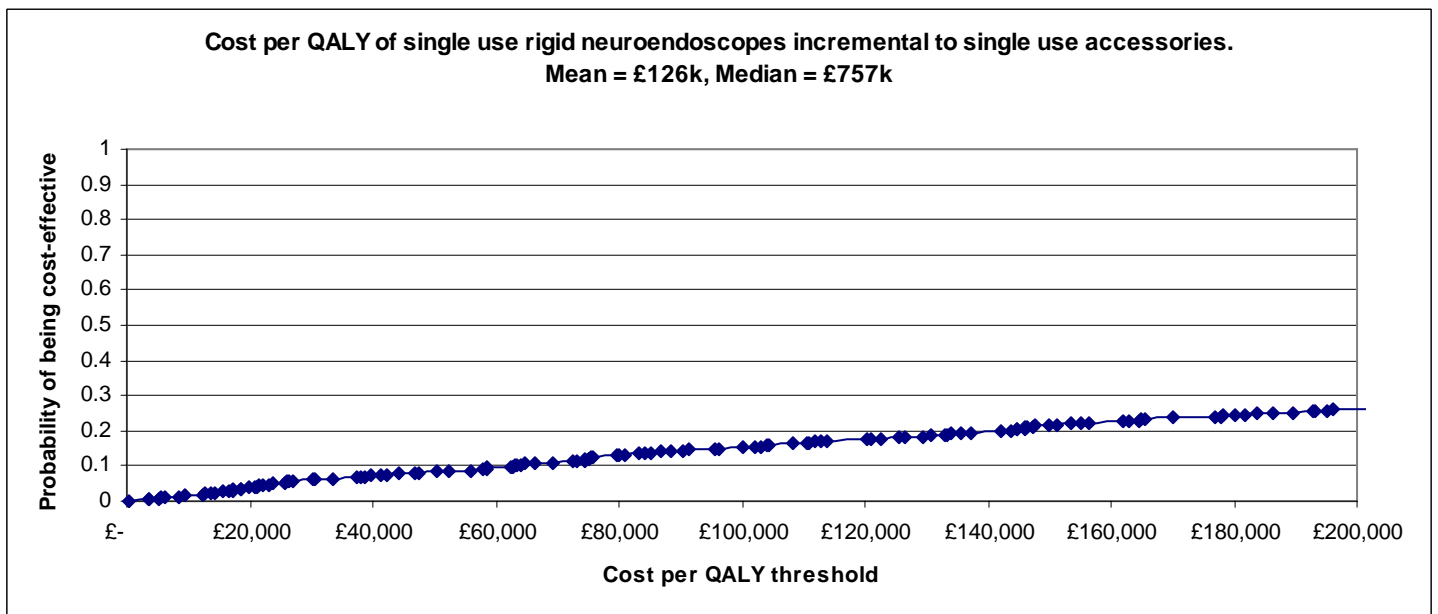
The 95% reference range for each specialty as taken from the CEAC and is derived from the 2.5% and the 97.5% points

Figure 8: The CEAC for single-use accessories with re-useable rigid neuroendoscopes



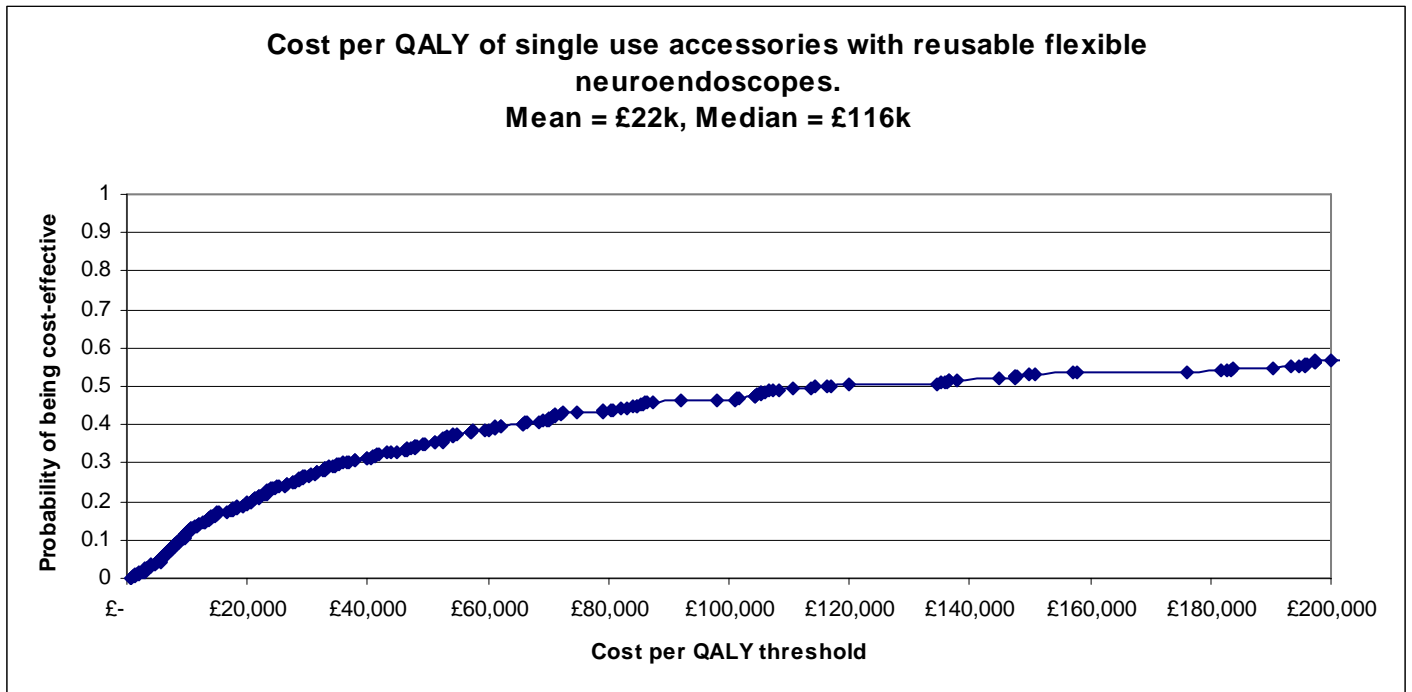
Proportion of times cost per QALY is below £30,000 = 40%

Figure 9: The CEAC for single-use rigid neuroendoscopes having decided on single-use accessories



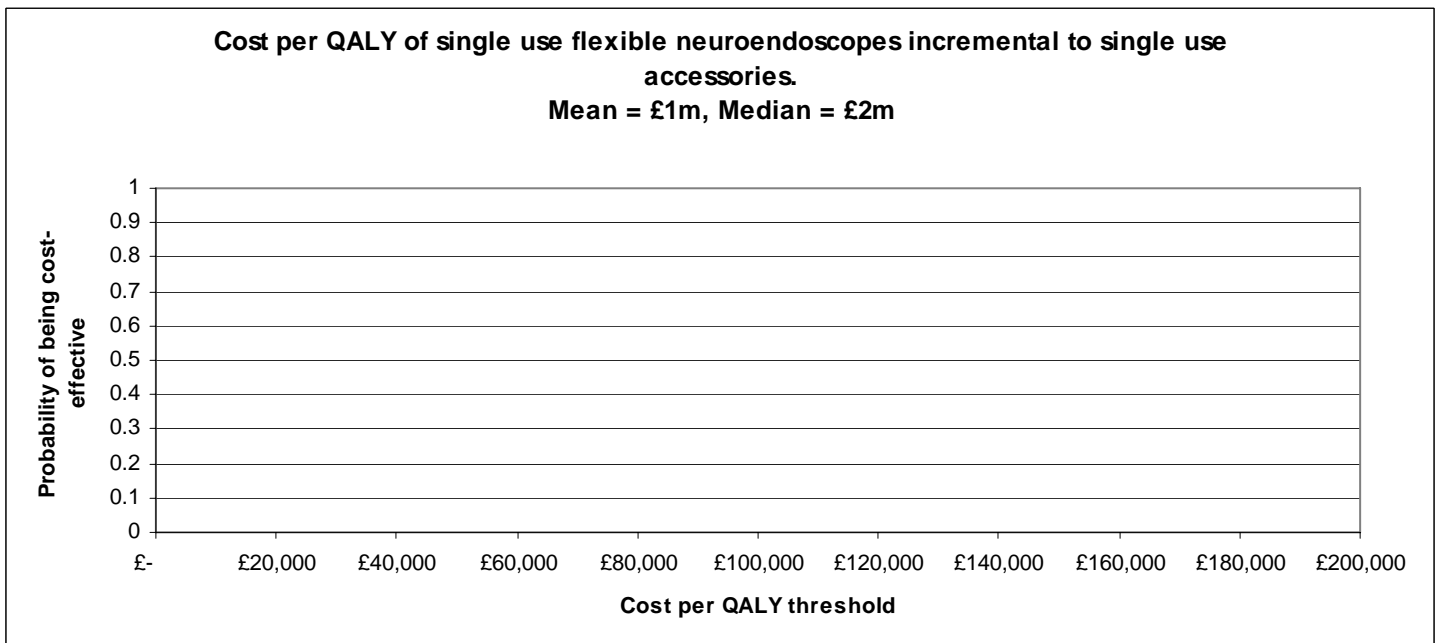
Proportion of times cost per QALY is below £30,000 = 6%

Figure 10: The CEAC for single-use accessories with re-useable flexible neuroendoscopes



Proportion of times cost per QALY is below £30,000 = 27%

Figure 11: The CEAC for single-use flexible neuroendoscopes having decided on single-use accessories



Proportion of times cost per QALY is below £30,000 = 0%

Note that all cost per QALY ratios were greater than £200,000 in this analysis.

Analysis of the distribution of QALY loss and the number of deaths expected when re-usable instruments are maintained and targeted approaches are adopted.

The distributions of simulated deaths per specialty per modelling area over the 5-year results collection period are shown in Figures 12 to 15 for brain and posterior eye assuming that no additional single use instruments are used, and assuming that single-use instruments would be targeted at those patients returning to surgery. Figures 16 and 17 present the distribution of simulated deaths from rigid neuroendoscopy and flexible neuroendoscopy, assuming that both the neuroendoscope and the accessory were re-usable, and where the accessory was made single use.

This analysis has omitted spinal cord operations as the number of deaths was never greater than 1.5 in any of the 1000 parameter sets, even where instrument migration was allowed to continue. The numbers of deaths provided are grouped by the year of infection rather than the year of death, so a proportion of these deaths are expected to occur beyond the 5-year results collection period.

Similarly to the cost-effectiveness data the majority of simulations produce few deaths. However a small number of scenarios are associated with a large number of deaths. Instrument migration is associated with a greater number of deaths.

Descriptive statistics are given in Table 17 for brain and posterior eye operations and in Table 18 for neuroendoscopy.

Figure 12: The distribution of simulated deaths due to iatrogenic CJD per modelling area over 5 years for brain surgery

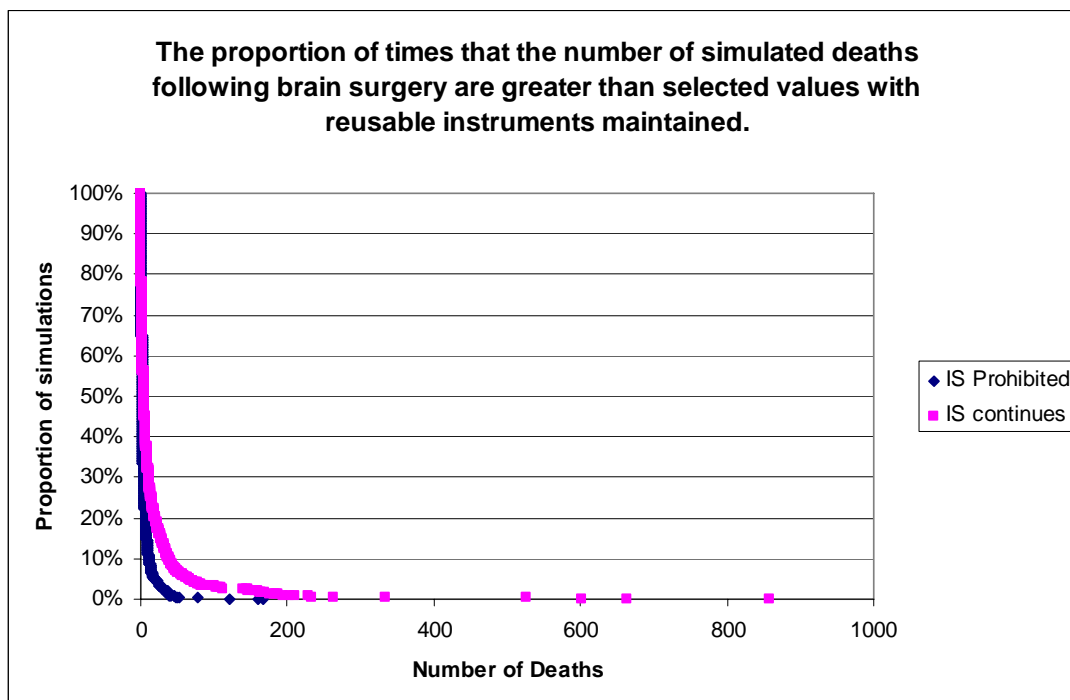


Figure 13: The distribution of simulated deaths due to iatrogenic CJD per modelling area over 5 years for brain surgery when single use instruments are targeted at patients with previous brain surgery

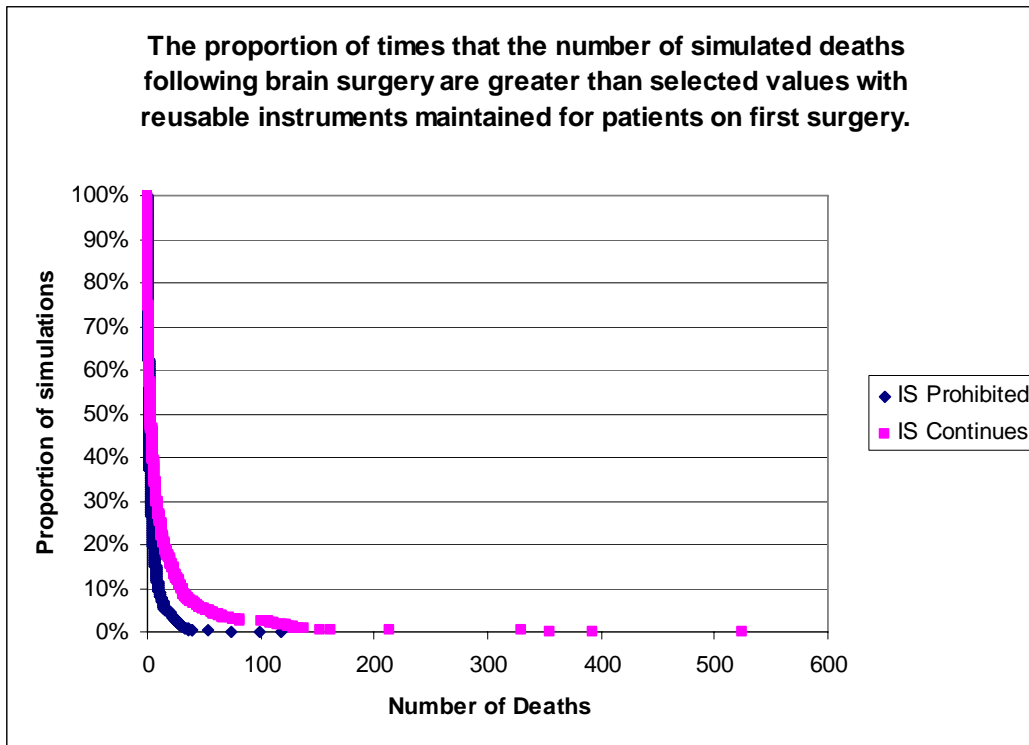


Figure 14: The distribution of simulated deaths due to iatrogenic CJD per modelling area over 5 years for posterior eye surgery

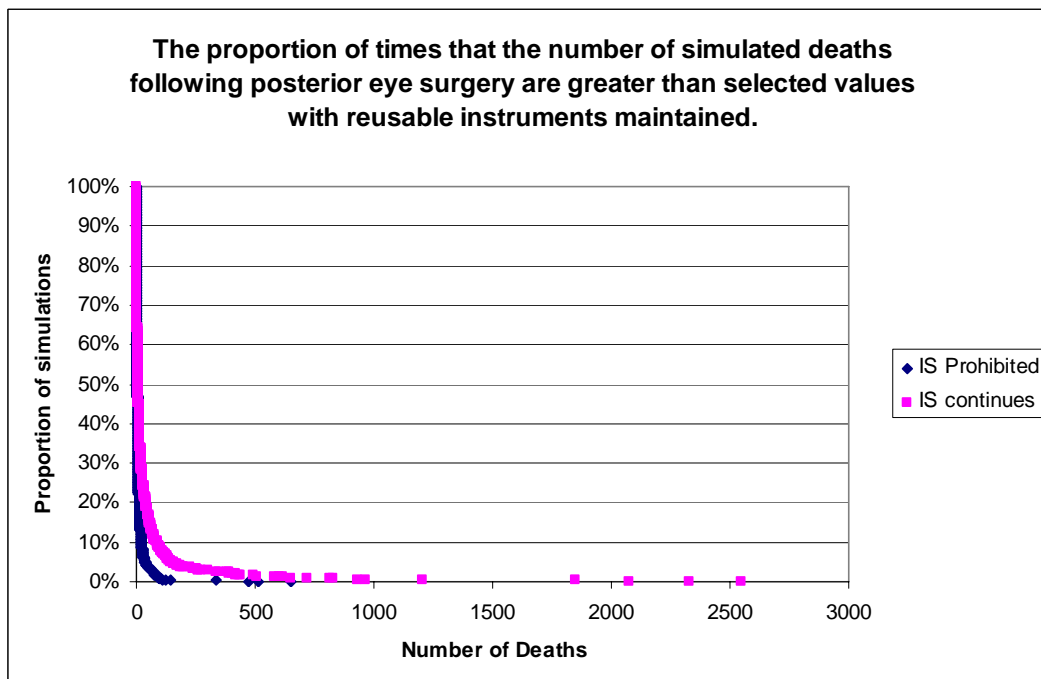


Figure 15: The distribution of simulated deaths due to iatrogenic CJD per modelling area over 5 years for brain surgery when single use instruments are targeted at patients with previous posterior eye surgery

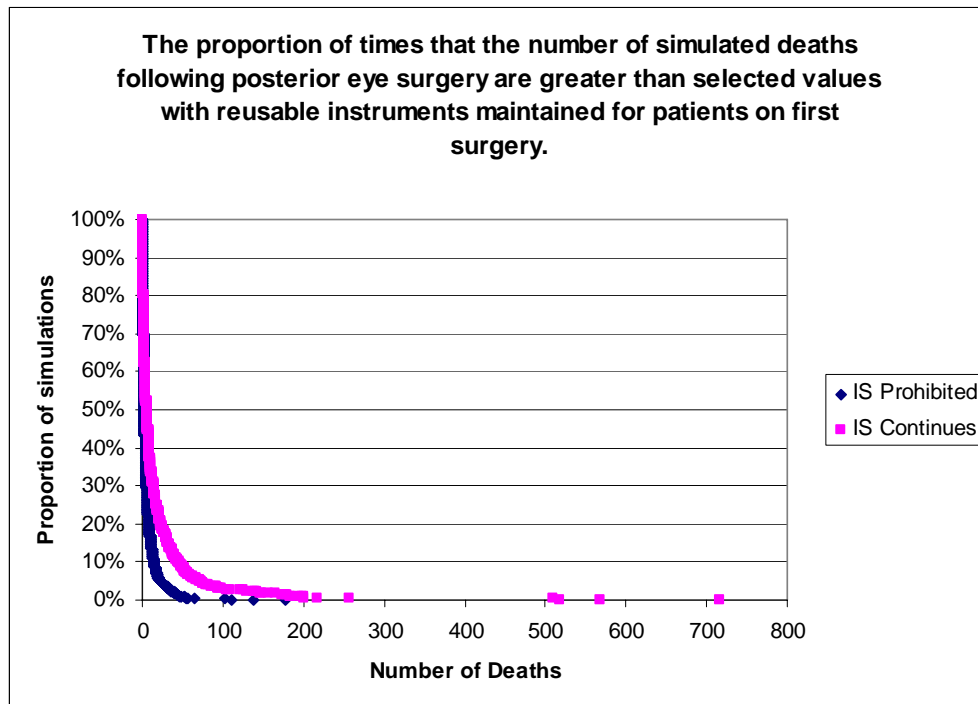


Table 17. A summary of the distribution of the expected number of deaths in brain and posterior eye operations assuming re-usable instruments.

Percentile	Brain		Posterior Eye	
	Instrument Migration Continues	Instrument Migration Prohibited	Instrument Migration Continues	Instrument Migration Prohibited
1%	0.00	0.00	0.00	0.00
2.5%	0.02	0.02	0.00	0.00
5%	0.08	0.04	0.02	0.02
10%	0.34	0.22	0.26	0.14
25%	1.40	0.74	1.54	0.74
50% (median)	4.74	1.88	7.92	3.00
75%	15.16	5.14	29.80	8.88
90%	39.00	10.66	87.04	20.78
95%	65.80	18.12	152.34	36.10
97.5%	140.42	30.70	348.50	68.52
99%	194.70	39.18	653.68	94.82

Due to the increased number of deaths following instrument migration, CJDAS assumed that this would be prohibited by guidance, the purchasing of additional supplementary instruments that become part of sets and better tracking methods. As such the report focuses on analyses where instrument migration has been prohibited.

Figure 16: The distribution of simulated deaths due to iatrogenic CJD per modelling area over 5 years for rigid neuroendoscopy with re-useable instruments

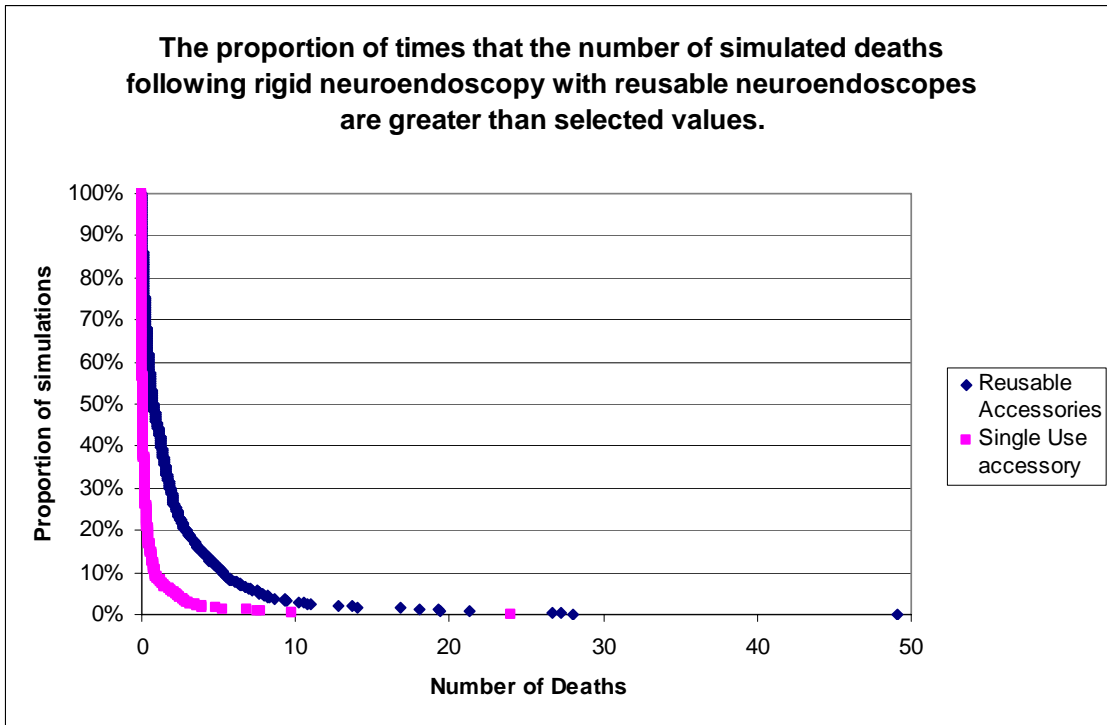


Figure 17: The distribution of simulated deaths due to iatrogenic CJD per modelling area over 5 years for flexible neuroendoscopy with re-useable instruments

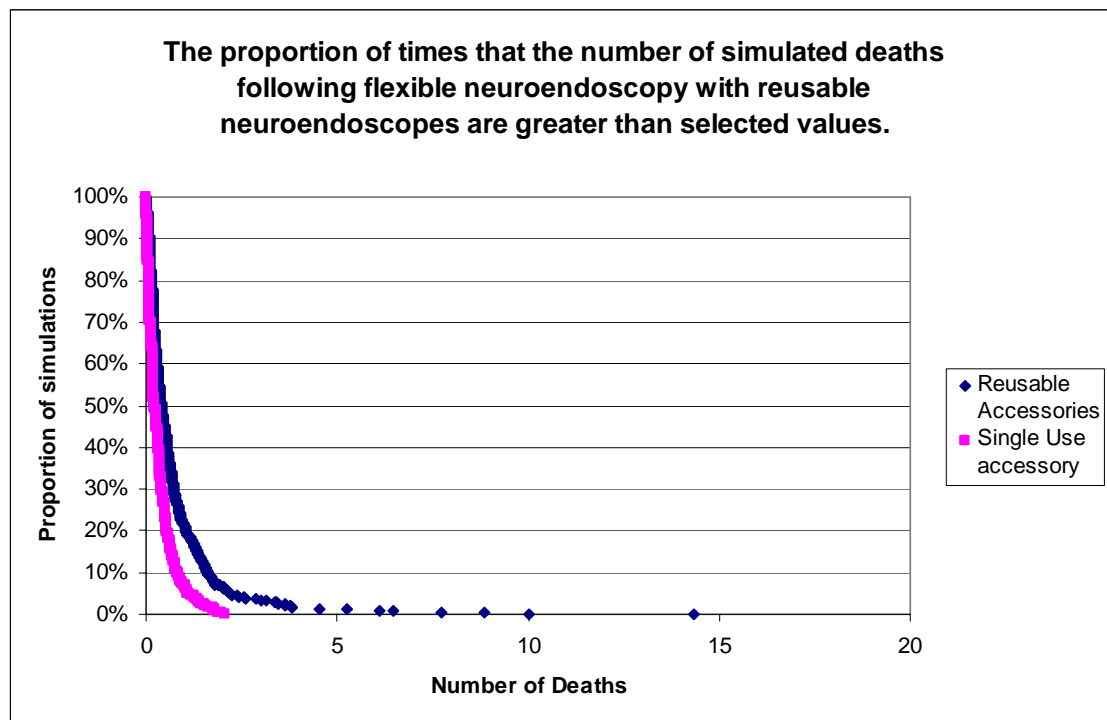


Table 18. A summary of the distribution of the expected number of deaths in neuroendoscopy.

Percentile	Rigid Neuroendoscope (NE)		Flexible Neuroendoscope (NE)	
	Both NE and accessories reusable	NE re-usable with single-use accessories	Both NE and accessories reusable	NE re-usable with single-use accessories
1%	0.00	0.00	0.00	0.00
5%	0.00	0.00	0.06	0.06
10%	0.02	0.00	0.10	0.06
25%	0.18	0.00	0.20	0.12
50% (median)	0.70	0.08	0.44	0.26
75%	2.12	0.30	0.92	0.52
90%	5.12	0.84	1.66	0.82
95%	7.52	1.98	2.22	1.10
99%	18.84	6.68	6.28	1.80

CJDAS decided that the introduction of single use neuroendoscopic accessories was cost-effective, however making neuroendoscopes single use was not.

5 Budget Impact

CJDAS decided that the neuroendoscopic accessories should become single-use. Despite some risks of secondary infection following contaminated surgical instruments, the large costs of replacing brain, spinal cord and posterior eye sets were not cost-effective.

In addition to expenditure on single use instruments the costs involved in prohibiting instrument migration must also be considered. However the logistics of doing this could range from computerised scanning systems or from a more diligent workforce coupled with the purchase of more instruments per set to remove the need for supplementary instruments. As such the costs associated with the prohibition of instrument migration have not been estimated.

For these analyses we have assumed that the costs of neuroendoscopic accessories remains at £200 each throughout the duration of the modelling period. Any reduction in costs that could occur through mass production, as has been seen in gastro-intestinal biopsy forceps have been ignored in our analyses, and thus these may represent over-estimates of the true costs.

Gross costs of instrument purchase.

The gross cost of purchasing single-use accessories for neuroendoscopes for all operations is estimated in Table 19. It is estimated that 87% of this expenditure will be borne by the NHS, with 13% being borne by the private sector.

Table 19: The estimated gross costs due to the purchase of single-use neuroendoscopic accessories

Specialty	Operations per year per modelling area	Cost per set of re-usable instruments (£)	Gross Budget Implication at re-usable prices. (£k)
Annual Neuroendoscopy accessories cost	25	200	5.00
Annual cost per modelling area			5.00
Annual cost for England and Wales			135.00
Annual cost for the UK *			152.42
5-year cost for the UK †			712.25

* Assuming that the population of Scotland and Northern Ireland is 12.9% that of England and Wales, (<http://www.statistics.gov.uk>) and that costs are proportional to population.

† Costs discounted at 3.5% per annum.

Expected net costs of single-use instrument purchase.

The net costs of purchasing single-use accessories for neuroendoscopes, including the costs of treating patients with CJD that are avoided, is estimated in Table 20. It is estimated that 87% of this expenditure will be borne by the NHS, with 13% being borne by the private sector. The net costs will be slight underestimates as we have assumed that prevented costs of clinical CJD will occur in the year the patient was infected, rather than the year of onset and due to discounting costs these will be overestimated. All costs are discounted at 3.5% per annum.

Table 20: The estimated gross costs due to the purchase of single-use neuroendoscopic accessories

Specialty	Instrument Migration prohibited	
	Expected costs avoided due to the reduction in CJD cases over 5 year (£k)	Net Budget Implication over 5 years (£k)
Neuroendoscopy accessories		
5-Year cost per modelling area	1.194	22.171
5-Year cost for England and Wales	32.312	598.628
5-Year cost for the UK *	36.390	675.851

* Assuming that the population of Scotland and Northern Ireland is 12.9% that of England and Wales, (<http://www.statistics.gov.uk>) and that costs are proportional to population.

6 Conclusions

The range in the cost per QALY values shows the great deal of uncertainty associated with the modelled results. Given the current assumptions and input parameter distributions, a large number of iatrogenic CJD cases caused through surgical procedures cannot be ruled out, however the majority of simulations produce relatively small numbers of secondary infections. The availability of improved information about key parameters (such as the prevalence of CJD in the community) would help evaluate the probability of a large number of cases.

The presence of instrument migration in brain and posterior eye surgery can greatly increase the expected number of secondary infections, and this should be prohibited wherever possible.

The mean cost per QALY ratios for the introduction of single-use instruments in brain surgery and posterior eye operations are generally greater than the £30,000 value that would be deemed cost-effective where instrument migration has been prohibited. However these cost-effectiveness ratios fall below £30,000 where instrument migration is assumed to continue at the currently estimated rate.

Basing policy purely on the mean cost per QALY values will require a judgment on whether instrument migration can be prohibited in real-world settings. If this can be achieved then it is not cost-effective to dispose of reusable instruments after one use in brain or posterior eye surgery. It is however cost-effective to move to single use neuroendoscopic accessories. If instrument migration is assumed to continue at the presently estimated rate then single-use instruments are cost-effective in posterior eye operations, and a targeted approach is cost-effective in brain surgery, with re-usable instruments disposed of after use on a patient with a previous history of brain surgery. Again it is cost-effective to move to single use neuroendoscopic accessories.

These results have been calculated assuming that the costs of re-usable instruments remain at current prices. If these costs significantly fall due to mass production then the cost per QALY associated with a move to single-use instruments will fall, and the figures should be revised if this happens. Our analysis has also assumed that any single use instrument would be of equivalent quality to those re-usable instruments that are currently in use. Sensitivity analyses have shown that even small QALY losses associated with inferior single-use instruments can have a far greater effect than the QALYS assumed lost by iatrogenic CJD infections. As such where single use instruments are to be used, a rigorous procurement process must be enforced.

Appendices

Appendix 1 : Elicited distributions on current decontamination processes.

Part a) of Appendix 1 discusses the results of the elicitation process for unknown parameters that deal with the decontamination of surgical instruments. Part b) of Appendix 1 discusses the results of the elicitation process for unknown parameters that deal with the decontamination of neuroendoscopes and neuroendoscope accessories.

a) Results from the elicitation meeting on the decontamination of surgical instruments

This document details the elicitation process that was undertaken, mainly around the effects of decontamination. Expert attendees were

John Lumley

John Stephenson
Chief Research Officer, New and Emerging Vaccines, Department of Health

Don Jeffries
Department of Virology, St Bartholomew's Hospital and the Royal London School of Medicine and Dentistry

Wayne Spencer
Director, Spencer Nickson Ltd

Paul Holland
Sterile Services and Decontamination Manager, Kingston Hospital NHS Trust

Beverley McNeil
University Lecturer, Faculty of Health and Social Care, Canterbury Christ Church University

The following questions were asked in the elicitation process.

- 1) The log reduction in infectivity associated with autoclaving alone
- 2) The log reduction associated with subsequent autoclaving cycles
- 3) Current detergent log reduction infection
- 4) Subsequent levels of reduction in infectivity due to current detergents
- 5) Future detergent log reduction infection
- 6) Subsequent levels of reduction in infectivity due to future detergents
- 7) The proportion of mass that has already been through one complete decontamination process that is washed off in the next washing cycle
- 8) The proportion of mass existing on instruments following previous decontamination cycles that will be transferred to a patient in an operation

The distributions shown have relative densities shown on the y-axis. Since the probability under the line must equal 100%, peaks in the curve show the values, which are more likely. Lines that are fairly flat indicate that all values within the range have approximately equal probabilities of occurring, curves with a sharp peak indicate that the value at the peak is much more likely to occur than the remaining values.

A summary of the elicited distributions has been provided below.

Parameter	Distribution	10 th Percentile	Median	90% Percentile
1) The log reduction in infectivity associated with autoclaving alone	Normal: mean 2.5, variance 0.551	1.55	2.50	3.45
2) The log reduction associated with subsequent autoclaving cycles. Expressed as a proportion of 1)	Beta (3.546,18.969). mean 0.156, variance 0.006	0.07	0.15	0.26
3) Current detergent log reduction infection	Gamma (1.449,2.255). mean 0.642, variance 0.285	0.12	0.50	1.35
4) Subsequent levels of reduction in infectivity due to current detergents. Expressed as a proportion of 3)	Beta (1.372,1.522). mean 0.474, variance 0.064	0.13	0.50	0.83
5) Future detergent log reduction infection	Comment that a number of detergents with a log reduction of 6 are likely to be available in the relatively near future.			
6) Subsequent levels of reduction in infectivity due to future detergents. Expressed as a proportion of 5)	Beta (0.675,10.212). mean 0.062, variance 0.005	0.003	0.05	0.16
7) The proportion of mass that has already been through one complete decontamination process that is washed off in the next washing cycle	Beta (0.651, 70.451). mean 0.009, variance 0.0001	0.0004	0.005	0.02
8) The proportion of mass existing on instruments following previous decontamination cycles that will be transferred to a patient in an operation	Beta (0.750, 1.629). mean 0.315, variance 0.064	0.03	0.25	0.70

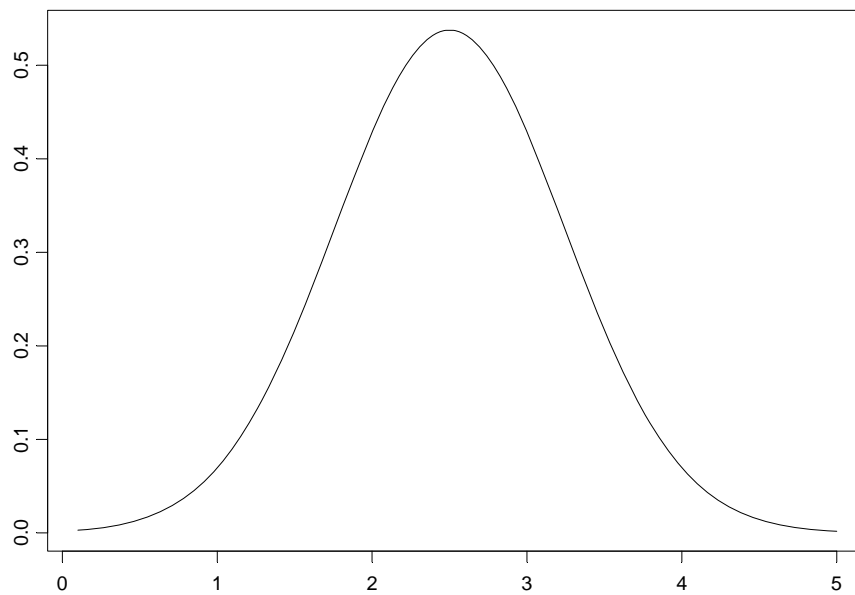
1) Parameter definition: the log reduction in infectivity associated with autoclaving alone.

Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
2	2.5	3

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.77	1.55	3.45	4.23



2) Parameter definition: The log reduction associated with second and subsequent autoclaving cycles, expressed as a proportion (between 0 and 1) of the log reduction achieved at the first cycle. This parameter is the relative effect of subsequent autoclavings of material after the first decontamination cycle.

There was more uncertainty in what level of log reduction in infectivity is achieved on subsequent autoclaving cycles. The variable was elicited based on assuming that the log reduction in the second autoclave cycle could not be more than the log reduction in the first cycle.

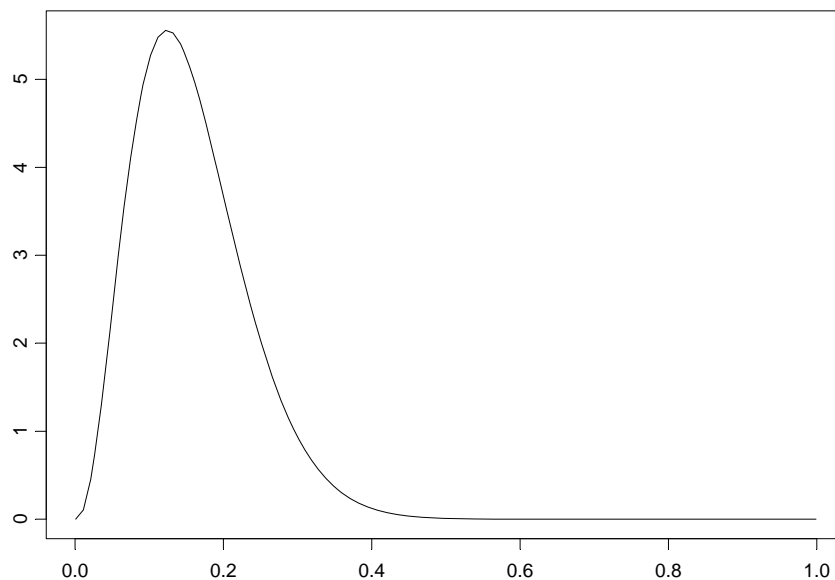
The values elicited from the experts were as follows. It was noted that the values are comparatively low and that this reflected the view that once material had been baked on during the first autoclaving cycle, there would be significantly less reduction in infectivity.

Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
0.10	0.15	0.20

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.03	0.07	0.26	0.37



3) Parameter definition: Current detergent log reduction infection

There was great uncertain in the level of infectivity reduction that the detergent used in current practice has. The elicited values were as follows.

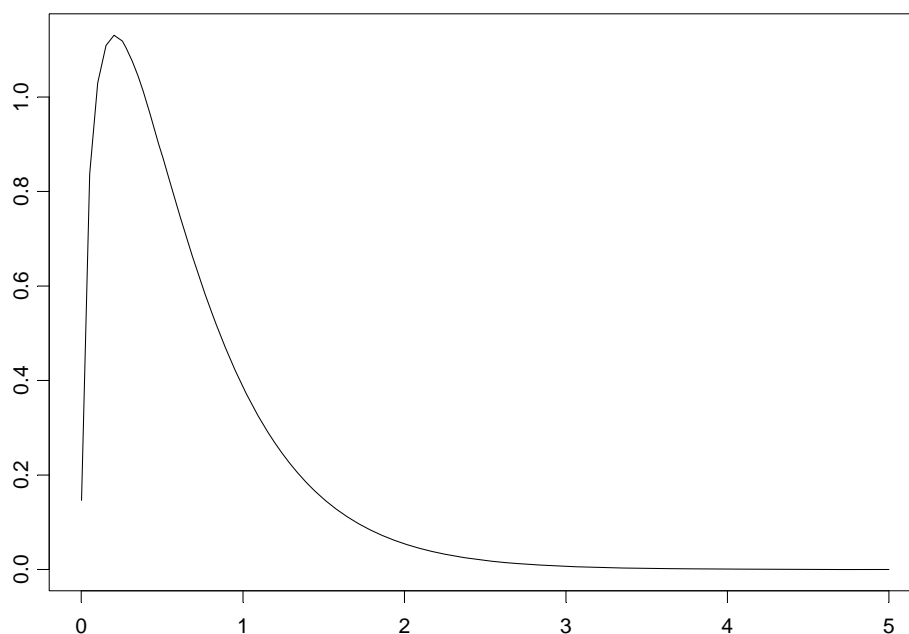
Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
0.01*	0.5	0.9

*This was difficult to reconcile with the other judgments, (25% chance less than 0.01, 25% chance between 0.01 and 0.5, 25% chance between 0.5 and 0.9), and so was not used when fitting the distribution.

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.02	0.12	1.35	2.45



4) Parameter definition: subsequent levels of reduction in infectivity due to current detergents

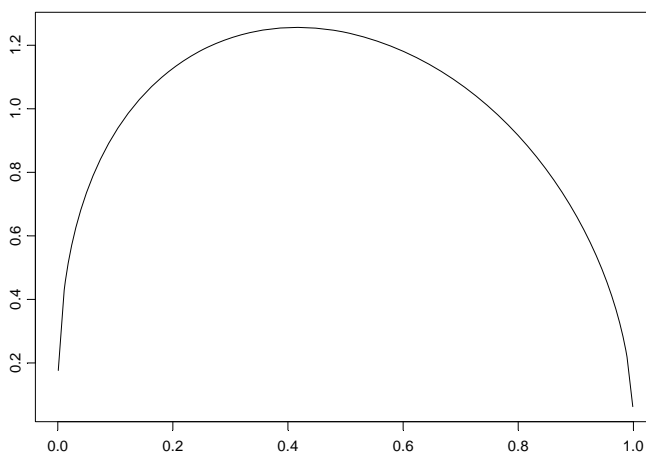
This was again expressed as a proportion of the reduction achieved by the first detergent level. Thus this must be between 0 and 1 and denotes the additional effect of subsequent detergent cycles compared with the first detergent cycle. The elicited values are below, the shape of the distribution is due to the uncertainty of the experts in this parameter.

Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
0.25	0.50	0.65

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.02	0.13	0.83	0.96



5) Parameter definition: Future detergent log reduction infection

Members of the elicitation group believed that new interventions and techniques for decontamination of prions were currently in relatively advanced stages of research, and that these would have an expected infectivity reduction of 6-log. The companies responsible for these interventions and techniques were contacted and submissions invited. A conservative 5-log reduction was used in the analyses, with a conservative time of 5-years assumed before widespread adoption in the NHS.

6) Parameter definition: subsequent levels of reduction in infectivity due to future detergents

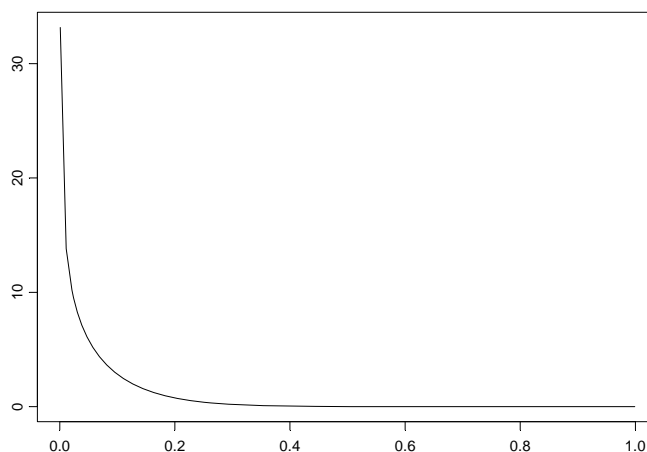
This parameter was defined as the relative effect of future detergents relative to the infectivity reduction achieved by the detergent on first use, thus any value between 0 and 1 could be chosen..

Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
0.01	0.05	0.07

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
1.0E-04	3.0E-03	0.16	0.32



7) Parameter definition: The proportion of mass that has already been through one complete decontamination process that is washed off in the next washing cycle.

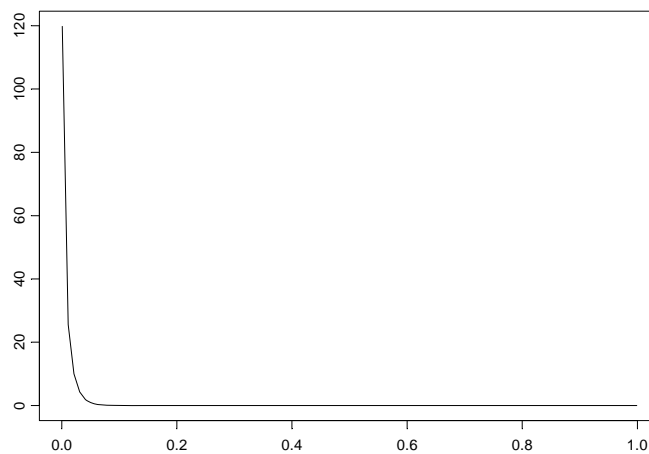
This parameter was defined as a proportion of total residual mass, thus any value between 0 and 1 could be chosen. The elicited values are at the low end of the range and demonstrate that the experts believe that mass that has become fixed to instruments during a decontamination cycle will be very resistant to further washing.

Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
0.0025	0.005	0.01

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
1.0E-05	4.0E-04	0.02	0.05



8) Parameter definition: The proportion of mass existing on instruments following previous decontamination cycles that will be transferred to a patient in an operation.

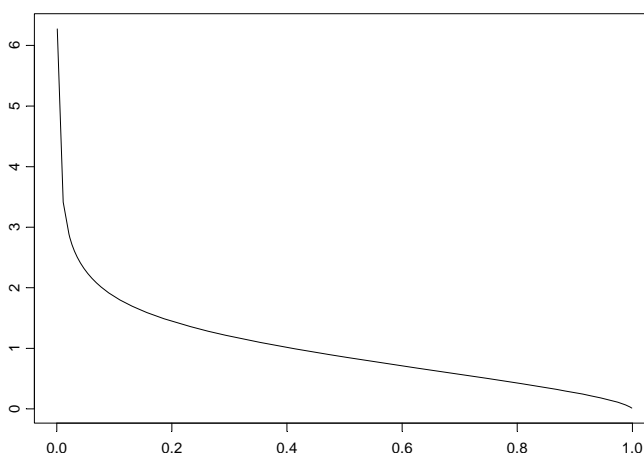
This parameter was defined as a proportion of total mass, thus any value between 0 and 1 could be chosen. The uncertainty in this variable was reasonably large.

Elicited judgments:

25 th percentile	50 th percentile	75 th percentile
0.10	0.25	0.50

Feedback

1 st percentile	10 th percentile	90 th percentile	99 th percentile
1.0E-03	0.03	0.70	0.93



b) Results from the elicitation meeting on the decontamination of neuroendoscopes and neuroendoscopic accessories.

Date of elicitation : 3rd April 2006.

Expert Attendees : Mike Bramble
Visiting Professor, University of Durham.

Laurian Cotes
Senior Theatre Nurse, University Hospital Nottingham

Don Jeffries
Department of Virology, St Bartholomew's Hospital and the Royal London
School of Medicine and Dentistry

Iain Robertson
Neurosurgeon, University Hospital Nottingham

Barrie White
Neurosurgeon, University Hospital Nottingham

Format of the meeting : The participants were given a tutorial describing how elicitation is undertaken and potential known biases that may occur.

7 questions were asked for which data was elicited. These were

- 1) The percentage of mass within a lumen that is picked up by a neuroendoscopic accessory or scraped off when being passed down the lumen.
- 2) The proportion of the mass from part 1) that will transfer to a patient and would present a risk of secondary infection if the mass was infectious.
- 3) The proportion of mass removed from the lumen and not transferred to the patient that remains adherent to the accessory.
- 4) The proportion of mass picked up from the lumen and still adhering to the accessory that will be reapplied to the lumen on withdrawal
- 5) The proportion of residual mass on the lumen once the accessory had been passed down and withdrawn, that will be removed following the decontamination process.
- 6) The proportion of mass on the outside of the neuroendoscope that is transferred to the patient.
- 7) The effect that the current cleaning process has on the infectivity of prions

These are summarised in the following table.

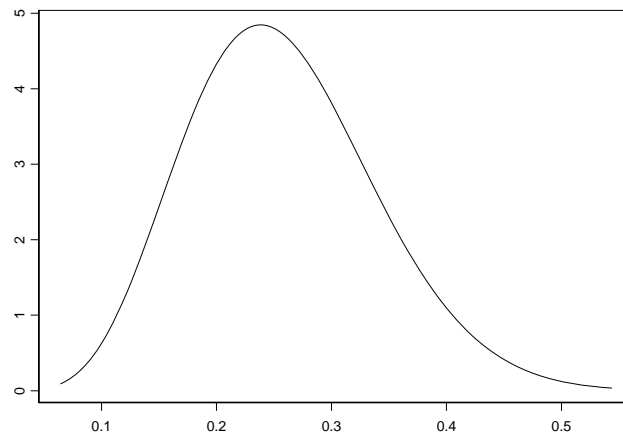
In addition some parameters were populated with single point estimates. These are detailed at the end of the document.

Parameter	Percentile				
	1 st	10 th	50 th	90 th	99 th
1) The percentage of mass within a lumen that is picked up by an neuroendoscopic accessory or scraped off when being passed down the lumen.	0.10	0.16	0.25	0.37	0.47
2) The proportion of the mass from part 1) that will transfer to a patient and would present a risk of secondary infection if the mass was infectious.	0.01	0.07	0.29	0.61	0.83
3) The proportion of mass removed from the lumen and not transferred to the patient that remains adherent to the accessory.	0.04	0.13	0.37	0.67	0.86
4) The proportion of mass picked up from the lumen and still adhering to the accessory that will be reapplied to the lumen on withdrawal	0.01	0.05	0.16	0.33	0.50
5) The proportion of residual mass on the lumen once the accessory had been passed down and withdrawn, that will be removed following the decontamination process.	0.57	0.73	0.88	0.97	0.99
6) The proportion of mass on the outside of the neuroendoscope that is transferred to the patient.	0.01	0.03	0.10	0.22	0.36
7) The effect that the current cleaning process has on the infectivity of prions	No effect assumed.				

1) The percentage of mass within a lumen that is picked up by an neuroendoscopic accessory or scraped off when being passed down the lumen.

Considerations

- That biofilm on the inside of the lumen is sticky
- That the tube is a snug fit for the accessory and that considerable contact may be made.



Fitted distribution: Beta(7.09298,20.45714). Mean = 0.258, variance = 0.00672

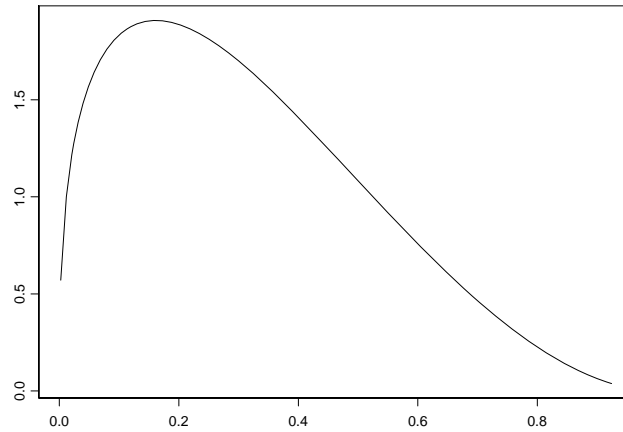
Percentiles:

1%	10%	50%	90%	99%
0.10	0.16	0.25	0.37	0.47

2) The proportion of the mass from part 1) that will transfer to a patient and would present a risk of secondary infection if the mass was infectious.

Considerations

- Some of the mass will remain adherent to the accessory, some will be washed away from the patient during the neuroendoscopic procedure.



Fitted distribution: Beta(1.364949, 2.894942). Mean = 0.320, variance = 0.0416

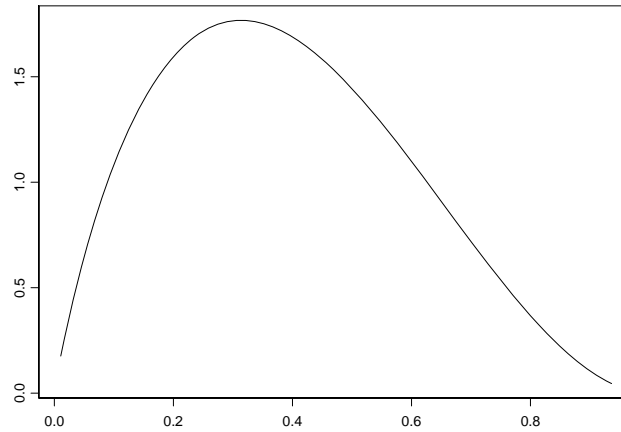
Percentiles:

1%	10%	50%	90%	99%
0.01	0.07	0.29	0.61	0.83

3) The proportion of mass removed from the lumen and not transferred to the patient that remains adherent to the accessory.

Considerations

- By definition (1- this parameter value) will be the amount of mass removed from the lumen and not transferred to the patient that will be washed away in the neuroendoscopic procedure.

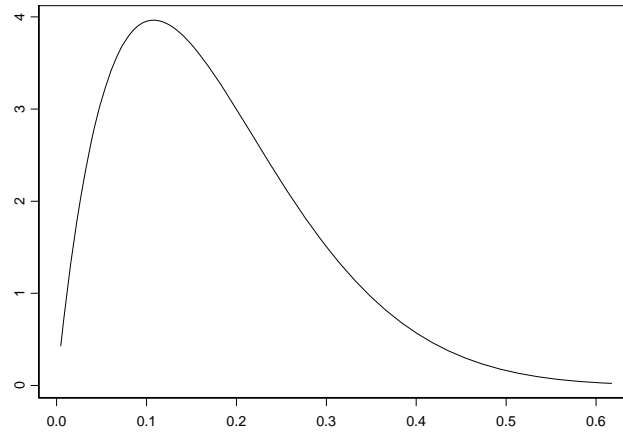


Fitted distribution: Beta(1.892514, 2.953072). Mean = 0.391, variance = 0.408.

Percentiles:

1%	10%	50%	90%	99%
0.04	0.13	0.37	0.67	0.86

4) The proportion of mass picked up from the lumen and still adhering to the accessory that will be reapplied to the lumen on withdrawal



Fitted distribution: Beta(1.984716, 9.142126). Mean = 0.402, variance = 0.404.

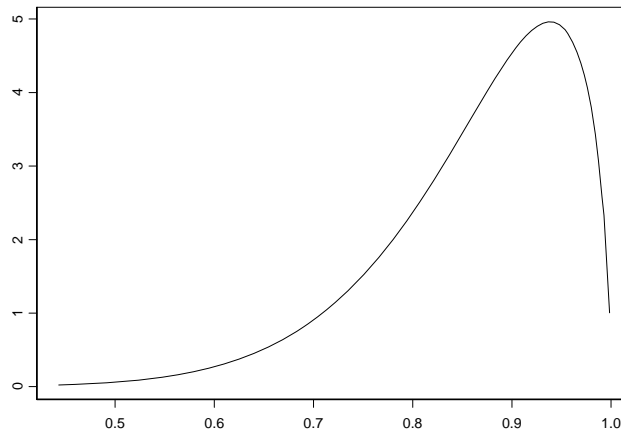
Percentiles:

1%	10%	50%	90%	99%
0.01	0.05	0.16	0.33	0.50

5) The proportion of residual mass on the lumen once the accessory had been passed down and withdrawn, that will be removed following the decontamination process.

Considerations

- The experts believed that brushing repeatedly removed 90% of all mass, with this proportion equally likely to apply to previously decontaminated mass, as it was to new mass harvested in a neuroendoscopic procedure.
- This distribution is assumed to be applicable to the removal of material from the outside of a neuroendoscope.

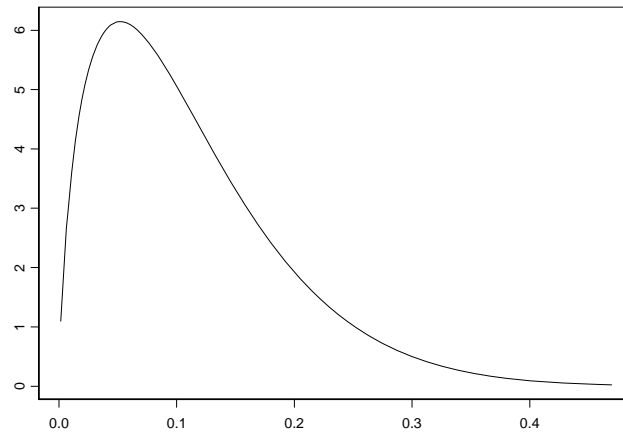


Fitted distribution: Beta(9.969138, 1.587379). Mean = 0.863, variance = 0.00941.

Percentiles:

1%	10%	50%	90%	99%
0.57	0.73	0.88	0.97	0.99

6) The proportion of mass on the outside of the neuroendoscope that is transferred to the patient.



Fitted distribution: Beta(1.663411, 13.107235). Mean = 0.113, variance = 0.00640.

Percentiles:

1%	10%	50%	90%	99%
0.01	0.03	0.10	0.22	0.36

7) The effect that the current cleaning process has on the infectivity of prions

Considerations

- The experts had no evidence to believe that solutions currently used in the cleaning process (e.g. ethylene oxide or chlorine dioxide) have any effect in deactivating prions.

The experts thus choose to assume no effect on infectivity from current cleaning solutions. Note this is at odds with a distribution elicited from a previous meeting, which had a median effectiveness of 0.5 log.

Single point parameters and further modelling assumptions.

- 1) 75% of neuroendoscopic procedures could be undertaken with rigid endoscopes without a change in practice
- 2) Additional procedures use neuroendoscopes which will not be coded into the HES data. These are pituitary removal and assisted operations with an estimation of 250 and 100 undertaken nationwide per annum respectively. In assisted operations accessories are not used, so mass would not be removed from the lumen.
- 3) That rigid neuroendoscopes can be autoclaved (although currently may not be in practice) however flexible endoscopes cannot.
- 4) Accessories used in rigid neuroendoscopes are autoclaved. Accessories used in flexible neuroendoscopes can be autoclaved but are not currently.
- 5) The median steady state mass on a lumen has been estimated as 14.1 μg . This has been derived assuming that there is a residual mass of $10\mu\text{g per cm}^2$ (taken from the pessimistic values in the Alfa paper¹⁰), that a tube has a diameter of 0.01cm and a length of 45 cm.
- 6) The median steady state mass on the outside of a neuroendoscope has been estimated as 12.6 μg . This has been derived assuming that there is a residual mass of $10\mu\text{g per cm}^2$ (taken from the pessimistic values in the Alfa paper), that a tube has a diameter of 0.04cm and a length of 10 cm that would be in contact with a patient.

Arbitrary ranges were put around the mass contained within a lumen and on the mass residing on the outside of a lumen. This allowed some investigation of the effect of changing the mass on the expected number of secondary infections.

¹⁰ Alfa MJ *et al* (1999): “Worst-case soiling levels for patient-used flexible endoscopes before and after cleaning” *Am J. Infect. Control* **27**, 392-401

Appendix 2 Results from the elicitation meeting on epidemiological parameters

The answers were primarily elicited from

Dr Robert Will, Consultant Neurologist
Professor James Ironside, Professor of Clinical Neuropathy
Mr Lester Firkins, Lay Co-Chair MRC Prion-1 Trial Steering Committee

Dr Hester Ward, Consultant in Epidemiology and Public Health sat through the training exercise and then reviewed the answers provided by the three main participants.

Information was elicited on the following parameters.

- 1) The number of asymptomatic individuals, aged 16-39 years, m-m homozygote at codon 129, that are currently incubating vCJD per million in this group in 2005.
- 2) The ratio of the proportion of asymptomatic individuals, aged 16-39 years, who are either m-v or v-v at codon 129 in relation to the proportion of asymptomatic individuals, aged 16-39, m-m homozygote at codon 129, that were incubating vCJD in 2005.
- 3) The ratio of the proportion of asymptomatic individuals, aged 40-69 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that were incubating vCJD in 2005.
- 4) The ratio of the proportion of asymptomatic individuals, aged 70 years and above, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that were incubating vCJD in 2005.
- 5) The ratio of the proportion of asymptomatic individuals, aged 0-15 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that were incubating vCJD in 2005..
- 6) The incubation period for an individual, irrespective of genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery.
- 7) The incubation period for an individual, with m-m homozygote at codon 129, with secondary infection from tonsil to tonsil surgery.
- 8) The incubation period for an individual, who is either m-v or v-v at codon 129, with secondary infection from tonsil to tonsil surgery.
- 9) The population median proportion of the incubation period in which the patient is infectious at lymph tissue

10) The population median proportion of the incubation period in which the patient is infectious at the central nervous system.

In the figure the values on the Y-axis can be largely ignored, however the higher the value the greater the probability of an event occurring, thus the peak of a curve will be the modal value.

Summary of elicited values

Parameter	Distribution	10 th Percentile	Median	90 th Percentile
1) The number of asymptomatic individuals, aged 16-39 years, m-m homozygote at codon 129, that were incubating vCJD per million in this group in 2005.	Beta(1.240, 2225.393)	84	400	1216
2) The ratio of the proportion of asymptomatic individuals, aged 16-39 years, who are either m-v or v-v at codon 129 in relation to the proportion of asymptomatic individuals, aged 16-39, m-m homozygote at codon 129, that were incubating vCJD in 2005.	Beta(1.238, 1.177)	0.14	0.50	0.88
3) The ratio of the proportion of asymptomatic individuals, aged 0-15 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that were incubating vCJD in 2005.	Beta(0.883, 4.015)	0.02	0.15	0.41
4) The ratio of the proportion of asymptomatic individuals, aged 40-69 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that that were incubating vCJD in 2005.	Beta(1.519, 5.396)	0.05	0.20	0.43
5) The ratio of the proportion of asymptomatic individuals, aged 70 years and above, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that that were incubating vCJD in 2005.	Beta(2.718, 47.313)	0.02	0.05	0.09
6) The incubation period for an individual, irrespective of genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery. (years)	Log normal, mean (on log scale): 0.693, s.d. (on log scale): 0.354	1 (2.5 th Percentile)	2	4 (97.5 th Percentile)
7) The incubation period for an individual, with m-m homozygote at codon 129, with secondary infection from tonsil to tonsil surgery. (years)	log normal, mean (on log scale): 2.076, s.d. (on log scale): 0.575	3 (5 th Percentile)	8	20 (95 th Percentile)
8) The incubation period for an individual, who is either m-v or v-v at codon 129, with secondary infection from tonsil to tonsil surgery. (years)	log normal, mean (on log scale): 2.993, s.d. (on log scale): 0.259	10 (5 th Percentile)	8	30 (95 th Percentile)
9) The population median proportion of the incubation period in which the patient is infectious at lymph tissue	Beta(166.212,41.808)	0.76	0.80	0.83
10) The population median proportion of the incubation period in which the patient is infectious at the central nervous system.	Beta (0.750, 1.629).	0.17	0.20	0.23

Parameter 1 description: number of asymptomatic individuals, aged 16-39 years, m-m homozygote at codon 129, that were incubating vCJD per million in this group in 2005.

Table 1.1: Elicited judgments

25 th percentile	50 th percentile	75 th percentile
200 (per million)	400	800

Comments:

These judgments were made in light of the Hilton study, though it was believed that the reported estimate was likely to be an underestimate of the true proportion.

Fitted distribution: Beta(1.240, 2225.393)

Table 1.2: Feedback from fitted distribution

1 st percentile	10 th percentile	90 th percentile	99 th percentile
12 (per million)	84	1216	2304

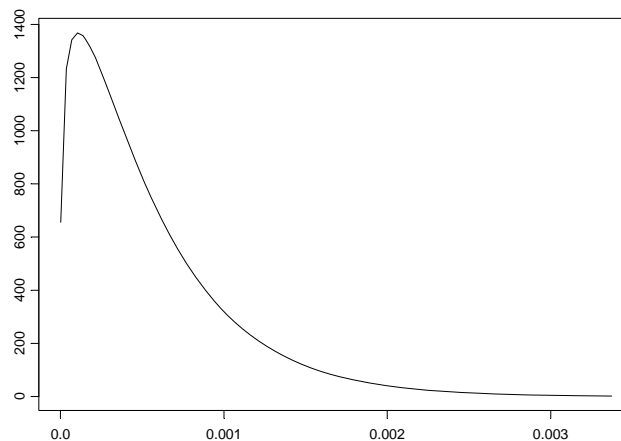


Figure 1: Fitted distribution for parameter 1

Note the axis here is the elicited value divided by a million, hence 0.001 would equate to 1000 patients per million.

2) Parameter 2 description: the ratio of the proportion of asymptomatic individuals, aged 0-15 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that are currently incubating vCJD.

It is assumed that this ratio is the same for pairs of age groups within the same genotype

Table 2.1: Elicited judgments

25 th percentile	50 th percentile	75 th percentile
0.5	0.15	0.25

Comments:

There are no cases observed in patients born since 1990

Fitted distribution: Beta(0.883, 4.015)

Table 2.2: Feedback from fitted distribution

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.001	0.02	0.41	0.66

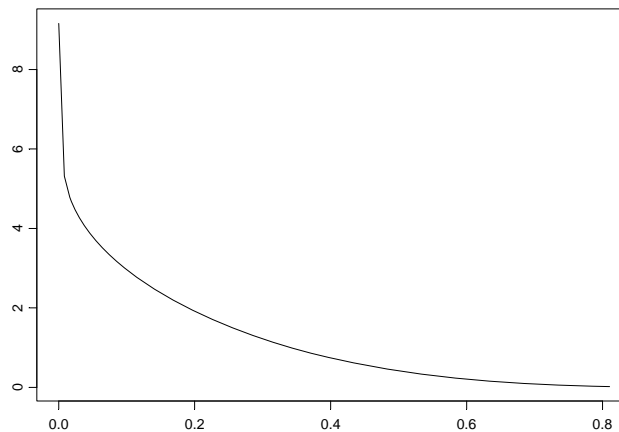


Figure 2: fitted distribution for parameter 2

To obtain the distribution of the absolute proportion for ages 0-15 and above, we can sample from the distributions of parameters 1 and 5 (and 2 for m-v/v-v genotypes) and multiply to obtain:

Table 2.3: the distribution of the absolute proportion for ages 0-15

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.2 (per million)	4	260	717

3) Parameter 3 description: the ratio of the proportion of asymptomatic individuals, aged 40-69 years, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that are currently incubating vCJD.

It is assumed that this ratio is the same for pairs of age groups within the same genotype

Table 3.1: Elicited judgments

25 th percentile	50 th percentile	75 th percentile
0.1	0.2	0.3

Fitted distribution: Beta(1.519, 5.396)

Table 3.2: Feedback from fitted distribution

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.01	0.05	0.43	0.64

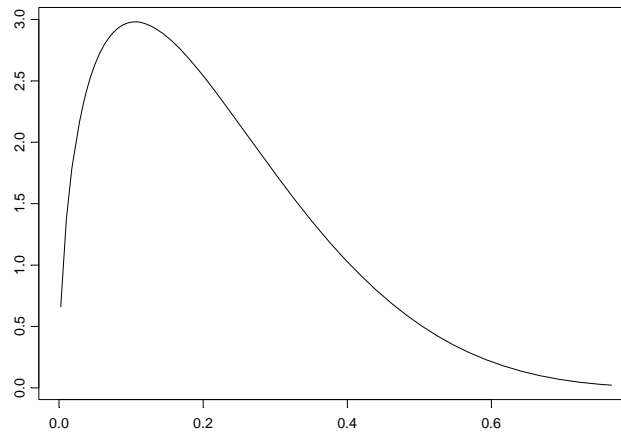


Figure 3: Fitted distribution for parameter 3

To obtain the distribution of the absolute proportion for ages 40-69, we can sample from the distributions of parameters 1 and 3 (and 2 for m-v/v-v genotypes) and multiply to obtain

Table 3.3: distribution of the absolute proportion for ages 40-69, m-m genotype

1 st percentile	10 th percentile	90 th percentile	99 th percentile
1 (per million)	9	299	740

4) Parameter 4 description: the ratio of the proportion of asymptomatic individuals, aged 70 years and above, that are currently incubating vCJD to the proportion of asymptomatic individuals, aged 16-39 years, that are currently incubating vCJD.

It is assumed that this ratio is the same for pairs of age groups within the same genotype

Table 4.1: Elicited judgments

25 th percentile	50 th percentile	75 th percentile
0.03	0.05	0.07

Fitted distribution: Beta(2.718, 47.313)

Table 4.2: Feedback from fitted distribution

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.01	0.02	0.09	0.15

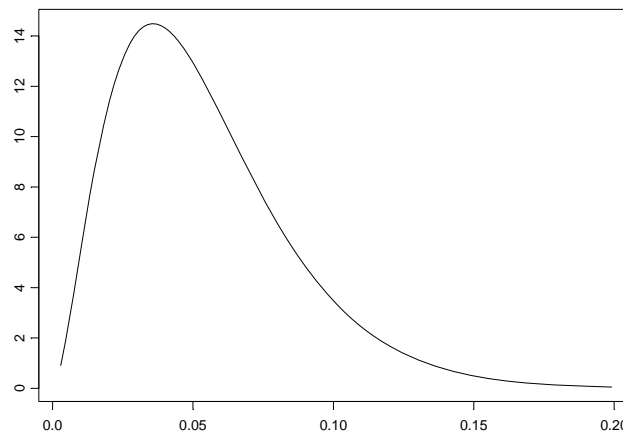


Figure 4: fitted distribution for parameter 4

To obtain the distribution of the absolute proportion for ages 70 and above, we can sample from the distributions of parameters 1 and 4 (and 2 for m-v/v-v genotypes) and multiply to obtain:

Table 4.3: the distribution of the absolute proportion for ages 70 and above, m-m genotype

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.4 (per million)	3	71	172

5) Parameter 5 description: the incubation period for an individual, irrespective of genotype at codon 129, with secondary infection from central nervous system to central nervous system surgery.

Note that the distribution required here describes uncertainty about individual incubation periods, rather than uncertainty about the population mean incubation period.

It is assumed that this distribution will be the same for all age groups and all genotypes.

Table 5.1: Elicited judgments

2.5 th percentile	50 th percentile	97.5 th percentile
1 (years)	2	4

Comment:

Judgments informed by observational data from sporadic iatrogenic transmission

Fitted distribution: log normal, mean (on log scale):0.693, s.d. (on log scale): 0.354

Table 5.2: Feedback from fitted distribution

1 st percentile	25 th percentile	75 th percentile	99 th percentile
0.9	1.6	2.5	4.6

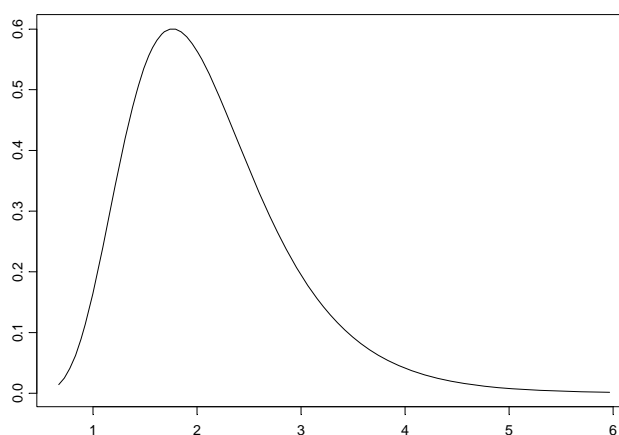


Figure 5: fitted distribution for parameter 5

Subsequent to the elicitation, new evidence became available that the incubation period would be greater for m-v and v-v genotypes. The above distribution was still thought credible for m-m patients, however the medians were increased to 7 and 12 years for m-v and v-v patients respectively. The standard deviation previously elicited was assumed to be applicable.

6) Parameter 6 description: the incubation period for an individual, with m-m homozygote at codon 129, with secondary infection from tonsil to tonsil surgery.

Note that the distribution required here describes uncertainty about individual incubation periods, rather than uncertainty about the population mean incubation period.

It is assumed that this distribution will be the same for all age groups

Table 6.1: Elicited judgments:

5 th percentile	50 th percentile	95 th percentile
3 (years)	8	20

Fitted distribution: log normal, mean (on log scale):2.076, s.d. (on log scale): 0.575

Table 6.2: Feedback:

1 st percentile	25 th percentile	75 th percentile	99 th percentile
2.1	3.8	16.7	30.3

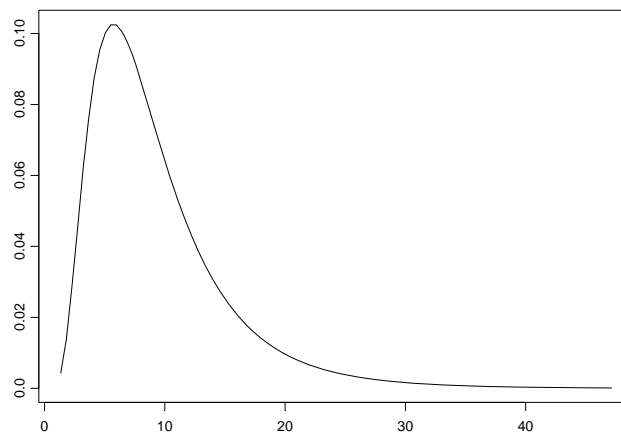


Figure 6: fitted distribution for parameter 6

7) Parameter 7 description: the incubation period for an individual, who is either m-v or v-v at codon 129, with secondary infection from tonsil to tonsil surgery.

Note that the distribution required here describes uncertainty about individual incubation periods, rather than uncertainty about the population mean incubation period.

It is assumed that this distribution will be the same for all age groups

Table 7.1: Elicited judgments

5 th percentile	50 th percentile	95 th percentile
10 (years)	20	30

Fitted distribution: log normal, mean (on log scale):2.993, s.d. (on log scale): 0.259

Table 7.2: Feedback from fitted distribution:

1 st percentile	10 th percentile	90 th percentile	99 th percentile
11	14	28	36

Note: the fitted 1st percentile is greater than the elicited 5th percentile. This adjustment is necessary if it believed that a skewed distribution is appropriate.

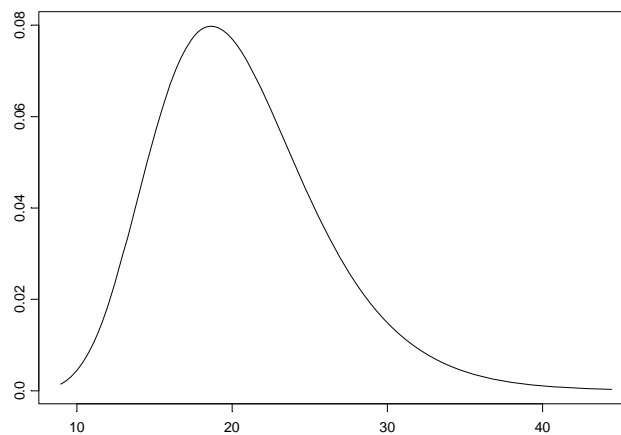


Figure 7: fitted distribution for parameter 7

8) Parameter 8 description: the population median proportion of the incubation period in which the patient is infectious at lymph tissue

Table 8.1: Elicited judgments

2.5 th percentile	50 th percentile	97.5 th percentile
0.7	0.8	0.85

Comments:

These judgments are based on extrapolation from animal models and are not thought to be inconsistent with observed data in vCJD appendices

Fitted distribution: Beta(166.212,41.808)

Table 8.2: Feedback from fitted distribution

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.73	0.76	0.83	0.86

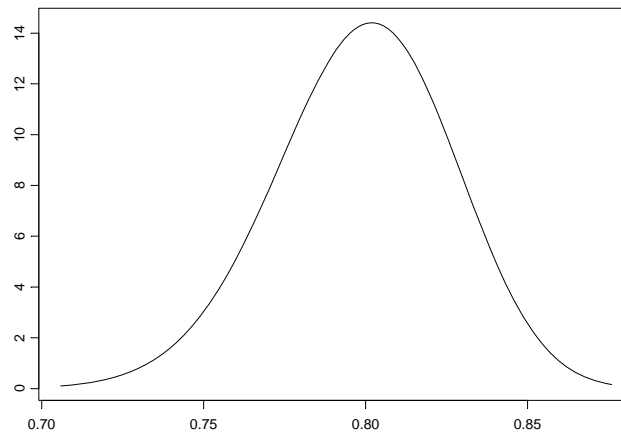


Figure 8: fitted distribution for parameter 8

9) Parameter 9 description: the population median proportion of the incubation period in which the patient is infectious at the central nervous system.

Table 9.1: Elicited judgments

2.5 th percentile	50 th percentile	97.5 th percentile
0.15	0.20	0.25

Comments:

These judgments are based on extrapolation from animal models.

Fitted distribution: Beta(50.126,199.646)

Table 9.2: Feedback from fitted distribution

1 st percentile	10 th percentile	90 th percentile	99 th percentile
0.15	0.17	0.23	0.26

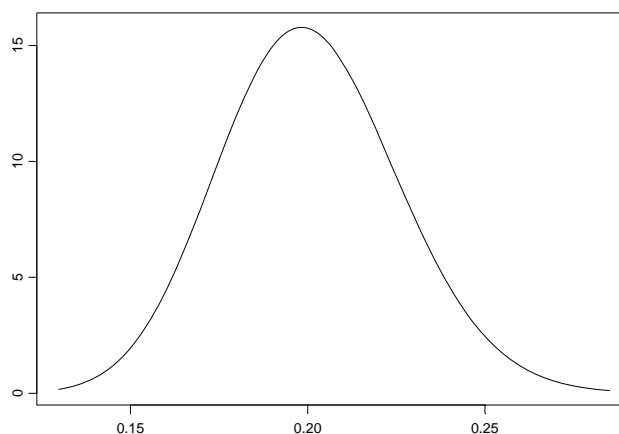


Figure 9: fitted distribution for parameter 9

Following the elicitation data new evidence became available that made the elicitation experts revise some of their previous distributions on the incubation time by genotype. The new distributions for m-v and v-v genotypes are produced below.

10) The assumed incubation period for a patient of genotype m-v infected at the central nervous system.

Lognormal Mean = 7.44 sd 2.69 ($\log X \sim N(1.946, 0.122^2)$)

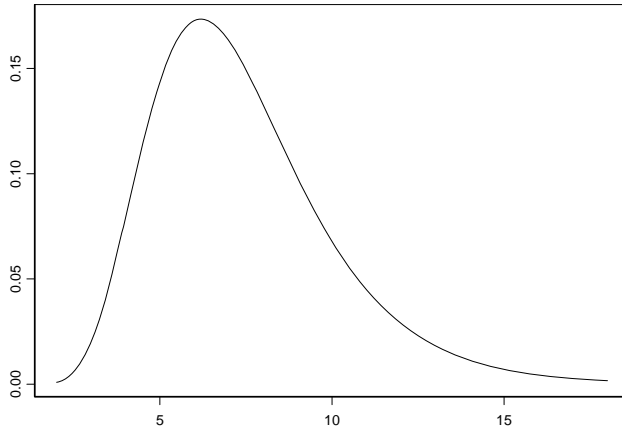


Figure 10: fitted distribution for parameter 10

Table 10.1: Feedback from fitted distribution

1%	10%	25%	50%	75%	90%	99%
3.107	4.475	5.531	7.000	8.859	10.951	15.771

11) The assumed incubation period for a patient of genotype m-v infected at the central nervous system.

Lognormal Mean = 12.80 sd 4.81 ($\log X \sim N(2.484, 0.132^2)$)

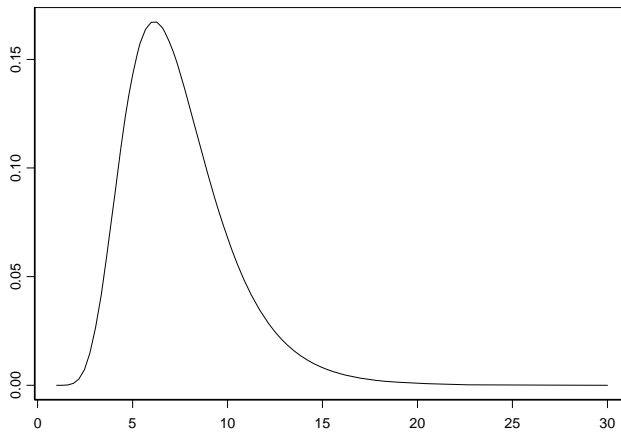


Figure 11: fitted distribution for parameter 11

Table 11.1: Feedback from fitted distribution

1%	10%	25%	50%	75%	90%	99%
5.147	7.525	9.382	11.989	15.320	19.103	27.927

12) The assumed susceptibility of patients of genotype m-v in displaying clinical symptoms once infected.

Uniform 0.4-0.6.

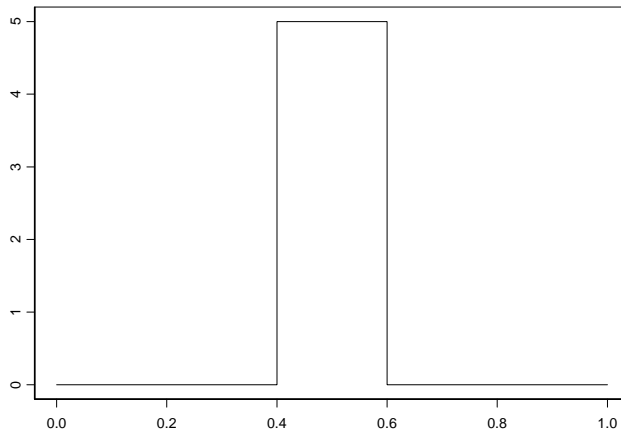


Figure 12: fitted distribution for parameter 12

Table 12.1: Feedback from fitted distribution

1%	10%	25%	50%	75%	90%	99%
0.402	0.420	0.450	0.500	0.550	0.580	0.598

13) The assumed susceptibility of patients of genotype m-v in displaying clinical symptoms once infected.

Uniform 0 – 0.4.

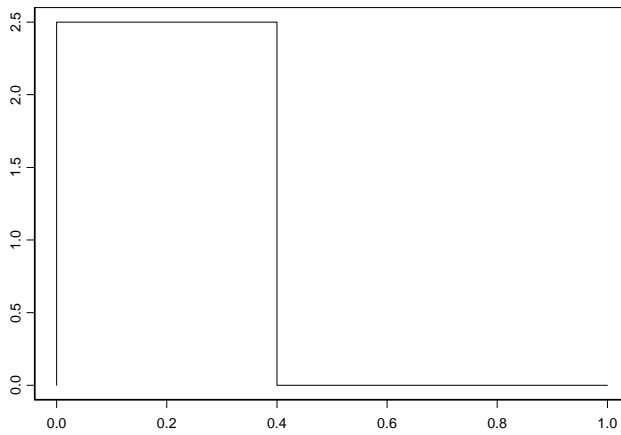


Figure 13: fitted distribution for parameter 13

Table 13.1: Feedback from fitted distribution

1%	10%	25%	50%	75%	90%	99%
0.004	0.040	0.100	0.200	0.300	0.360	0.396

Appendix 3: Operations included within the model

For each specialty, those HES (hospital episodes statistics) codes that are associated with tissue at risk of transmitting CJD are given.

The number of operations was calculated based on the number of main operations from the HES database with an additional 15% of operations assumed to be carried out within the private sector.

Brain Operations

The table below gives HES codes associated with intra-dural operations on the brain.

HES Code	Number of Operations per Year
A01 Major excision of tissue of brain	408
A02 Excision of lesion of tissue of brain	3197
A03 Stereotactic ablation of tissue of brain	1304
A04 Open biopsy of lesion of tissue of brain	475
A05 Drainage of lesion of tissue of brain	672
A07 Other open operations on tissue of brain	154
A08 Other biopsy of lesion of tissue of brain	1335
A09 Neurostimulation of brain	312
A10 Other operations on tissue of brain	322
A12 Creation of connection from ventricle of brain	1685
A13 Attention to component of connection from ventricle of brain	350
A14 Other operation on connection from ventricle of brain	1116
A16 Other open operations on ventricle of brain	215
A20 Other operations on ventricle of brain	1696
A22 Operations on subarachnoid space of brain	54
A24 Graft to cranial nerve	53
A25 Intracranial transection of cranial nerve	24
A26 Other intracranial destruction of cranial nerve	435
A27 Extracranial extirpation of vagus nerve (x)	24
A28 Extracranial extirpation of other cranial nerve	132
A29 Excision of lesion of cranial nerve	558
A30 Repair of cranial nerve	70
A31 Intracranial stereotactic release of cranial nerve	6
A32 Other decompression of cranial nerve	420
A33 Neurostimulation of cranial nerve	243
A34 Exploration of cranial nerve	23
A36 Other operations on cranial nerve	539
A38 Extirpation of lesion of meninges of brain	1174
A39 Repair of dura	243
A42 Other operations on meninges of brain	81
B01 Excision of pituitary gland	581
B02 Destruction of pituitary gland	5
B04 Other operations on pituitary gland	490
B06 Operations on the pineal gland	33
L33 Operations on aneurysm of cerebral artery	1229
L34 Other open operations on cerebral artery	75
Total	19,730

Adjustment for life expectancy based on poor prognosis.

Operations A01, A02, A04 and A08 were assumed to have prognoses with death within a 12 month period. It was assumed that 50% of patients who undergo A03, A05, A07 or A10 would also die within a 12-month period, with the remaining 50% having normal life expectancies. Those patients who died within a 12-month period were not assumed to become infectious before death.

Spinal Operations

The table below gives HES codes associated with operations on the spinal cord.

HES Code	Number of Operations per Year
A44 Partial extirpation of spinal cord	275
A45 Other open operations on spinal cord	56
A47 Other destruction of spinal cord	84
A48 Other operations on spinal cord	1181
A49 Repair of spina bifida	212
A51 Other operations on meninges of spinal cord	267
Total	2,075

Posterior Eye

The table below gives the HES codes that are assumed to be associated with high risk operations on the posterior eye.

HES Code	Number of Operations per Year
C79 Operations on vitreous body	15,274
C81 Photocoagulation of retina for detachment	1,620
C82 Destruction of lesion of retina	18,207
C84 Other operations on retina	1,423
Total	36,524

After completion of the initial set of runs, it was determined that C01 Excision of eye should have been included in this list. This would entail another 1,224 operations. However within C81 there are a number of operations where neither the retina nor the optic nerves are handled directly, and that should not be included. We have assumed that these approximately balance each other and that the 36,524 operations assumed to be at risk are correct.

ENT

Single use sets are already available for tonsillectomy and adenoidectomy. Given this the analysis of ENT was divided into operations where single use sets can be used and the remaining operations.

The tables below gives the HES codes that are assumed to be associated with tonsillectomy and adenoidectomy operations and those assumed to be associated with ENT operations which would contact medium risk tissue.

The HES codes associated with tonsillectomy and adenoidectomy operations

HES Code	Number of Operations per Year
E20 Operations on adenoids	8,051
F34 Excision of tonsil	58,111
F36 Other operations on tonsil	5,351
Total	71,513

The HES codes associated with remaining at risk ENT operations

HES Code	Number of Operations per Year
E19 Excision of pharynx	161
E21 Repair of pharynx	313
E23 Other open operations on pharynx	529
E27 Other operations on pharynx	1590
E29 Excision of larynx	621
E30 Open extirpation of lesion of larynx	48
E31 Reconstruction of larynx	398
E33 Other open operations on larynx	248
E38 Other operations on larynx	867
E39 Partial excision of trachea	32
E40 Plastic operation on trachea	37
E41 Open placement of prosthesis in trachea	127
E42 Exteriorisation of trachea	5997
E43 Other open operations on trachea	115
E44 Open operations on carina	36
F38 Extirpation of lesion of other part of mouth	3141
F39 Reconstruction of other part of mouth	85
F40 Other repair of other part of mouth	168
F42 Other operations on mouth	4313
F44 Excision of salivary gland	4948
F45 Extirpation of lesion of salivary gland	1106
F46 Incision of salivary gland	473
F48 Other operations on salivary gland	529
F50 Transposition of salivary duct	62
F51 Open extraction of calculus from salivary duct	501
F52 Ligation of salivary duct	8
F53 Other open operations on salivary duct	62
F55 Dilatation of salivary duct	141
F56 Manipulative removal of calculus from salivary duct	197
F58 Other operations on salivary duct	174
Total	27,027

Neuroendoscopy

The table below gives the HES codes that are assumed to be associated with high risk neuroendoscopic operations. In this table we used the all operations category rather than the main operation, as the difference was approximately 100, the number of operations thought to be assisted with a neuroendoscope used purely to aid viewing. In addition an additional 250 assisted pituitary removal operations that would not be within the HES data. These changes were made due to the advice of the neuroendoscopy experts used in the elicitation sessions (see Appendix 1)

HES Code	Number of Operations per Year
A17 Therapeutic endoscopic operations on ventricle of brain	267
A18 Diagnostic endoscopic examination of ventricle of brain	153
Additional use in pituitary removal	250
Total	670

It is assumed, based on expert advice, that currently 75% of these operations are undertaken with a rigid neuroendoscope, with the remaining 25% being undertaken with a flexible endoscope.

Adjustment for life expectancy based on poor prognosis.

No adjustments for mortality were made for this group with all patients assumed to have normal life expectancies. It has been assumed that all diagnostic endoscopic operations were assumed to carry a high risk.

Anterior Eye

The table below gives the HES codes that are assumed to be associated with medium risk operations on the anterior eye.

HES Code	Number of Operations per Year
C01 Excision of eye	1,064
C02 Extirpation of lesion of orbit	259
C03 Insertion of prosthesis of eye	175
C04 Attention to prosthesis of eye	357
C05 Plastic repair of orbit	376
C06 Incision of orbit	725
C08 Other operations on orbit	845
C53 Extirpation of lesion of sclera	13
C54 Buckling operations for attachment of retina	2,839
C55 Incision of sclera	286
C57 Other operations on sclera	417
C59 Excision of iris	237
C60 Filtering operations on iris	5,701
C61 Other operations on trabecular meshwork of eye	953
C62 Incision of iris	2,622
C64 Other operations on iris	420
C66 Extirpation of ciliary body	1,978
C67 Other operations on ciliary body	181
C69 Other operations on anterior chamber of eye	1,134
C71 Extracapsular extraction of lens	6,170
C72 Intracapsular extraction of lens	60
C73 Incision of capsule of lens	12,077
C74 Other extraction of lens	319
C75 Prosthesis of lens	336,617
C77 Other operations on lens	313
Total	376,135

Maxillo-Facial

The table below gives the HES codes that are assumed to be associated with medium risk operations within maxillo-facial.

HES Code	Number of Operations per Year
F01 Partial excision of lip	158
F02 Extirpation of lesion of lip	7,806
F03 Correction of deformity of lip	904
F04 Other reconstruction of lip	140
F05 Other repair of lip	4,515
F06 Other operations on lip	1,804
F08 Implantation of tooth	260
F09 Surgical removal of tooth	74,218
F10 Simple extraction of tooth	69,960
F11 Perprosthetic oral surgery	1,562
F12 Surgery on apex of tooth	5,093
F13 Restoration of tooth	3,371
F14 Orthodontic operations	4,350
F16 Other operations on tooth	2,550
F18 Excision of dental lesion of jaw	2,763
F20 Operations on gingiva	1,451
F22 Excision of tongue	473
F23 Extirpation of lesion of tongue	3,041
F24 Incision of tongue	3,315
F26 Other operations on tongue	3,006
F28 Extirpation of lesion of palate	1,235
F29 Correction of deformity of palate	1,411
F30 Other repair of palate	321
F32 Other operations on palate	3,755
Total	197,462

General Surgery

The table below gives the HES codes that are assumed to be associated with medium risk operations within general surgery.

HES Code	Number of Operations per Year
B18 Excision of thymus gland	163
B20 Other operations on thymus gland	21
B22 Excision of adrenal gland	396
B23 Operations on aberrant adrenal tissue	9
B25 Other operations on adrenal gland	202
B27 Total excision of breast	19,035
B28 Other excision of breast	40,902
B29 Reconstruction of breast	2,491
B30 Prosthesis for breast	3,067
B31 Other plastic operations on breast	7,726
B32 Biopsy of breast	5,063
B33 Incision of breast	2,638
B34 Operations on duct of breast	3,276
B35 Operations on nipple	3,628
B37 Other operations on breast	2,502
G01 Excision of oesophagus and stomach	1,461
G02 Total excision of oesophagus	145
G03 Partial excision of oesophagus	412
G04 Open extirpation of lesion of oesophagus	39
G05 Bypass of oesophagus	22
G06 Attention to connection of oesophagus	21
G07 Repair of oesophagus	301
G08 Artificial opening into oesophagus	70
G09 Incision of oesophagus	212
G10 Open operations on varices of oesophagus	69
G11 Open placement of prosthesis in oesophagus	53
G13 Other open operations on oesophagus	29
G21 Other operations on oesophagus	5,066
G23 Repair of diaphragmatic hernia	612
G24 Antireflux operations	3,229
G25 Revision of antireflux operations	147
G27 Total excision of stomach	665
G28 Open extirpation of lesion of stomach	1,413
G29 Open extirpation of lesion of stomach	225
G30 Plastic operations on stomach	323
G31 Connection of stomach to duodenum	35
G32 Connection of stomach to transposed jejunum	135
G33 Other connection of stomach to jejunum	1,209
G34 Artificial opening into stomach	6,049
G35 Operations on ulcer of stomach	796
G36 Other repair of stomach	199
G38 Other open operations on stomach	305
G40 Incision of pylorus	1,245
G41 Other operations on pylorus	51
G47 Intubation of stomach	2,287

G48 Other operations on stomach	711
G49 Excision of duodenum	67
G50 Open extirpation of lesion of duodenum	62
G51 Bypass of duodenum	138
G52 Operations on ulcer of duodenum	2,542
G53 Other open operations on duodenum	438
G57 Other operations on duodenum	24
G58 Excision of jejunum	367
G59 Extirpation of lesion of jejunum	33
G60 Artificial opening into jejunum	555
G61 Bypass of jejunum	85
G63 Other open operations on jejunum	162
G67 Other operations on jejunum	153
G69 Excision of ileum	4,260
G70 Open extirpation of lesion of ileum	360
G71 Bypass of ileum	483
G72 Other connection of ileum	311
G73 Attention to connection of ileum	129
G74 Creation of artificial opening into ileum	1,285
G75 Attention to artificial opening into ileum	4,791
G76 Intra-abdominal manipulation of ileum	327
G78 Other open operations on ileum	619
G82 Other operations on ileum	164
H01 Emergency excision of appendix	37,979
H02 Other excision of appendix	8,545
H03 Other operations on appendix	260
H04 Total excision of colon and rectum	909
H05 Total excision of colon	1,076
H06 Extended excision of right hemicolon	1,761
H07 Other excision of right hemicolon	9,509
H08 Excision of transverse colon	390
H09 Excision of left hemicolon	1,984
H10 Excision of sigmoid colon	4,203
H11 Other excision of colon	1,952
H12 Extirpation of lesion of colon	363
H13 Bypass of colon	259
H14 Exteriorisation of caecum	320
H15 Other exteriorisation of colon	6,102
H16 Incision of colon	112
H17 Intra-abdominal manipulation of colon	137
H19 Other open operations on colon	328
H30 Other operations on colon	1,003
H33 Excision of rectum	14,276
H34 Open extirpation of lesion of rectum	164
H35 Fixation of rectum for prolapse	480
H36 Other abdominal operations for prolapse of rectum	865
H40 Operations on rectum through anal sphincter	316
H41 Other operations on rectum through anus	4,507
H42 Perineal operations for prolapse of rectum	1,156
H44 Manipulation of rectum	6,494
H46 Other operations on rectum	1,786
J02 Partial excision of liver	1,419
J03 Extirpation of lesion of liver	406
J04 Repair of liver	105

J05 Incision of liver	138
J07 Other open operations on liver	38
J10 Transluminal operations on blood vessel of liver	547
J12 Other therapeutic percutaneous operations on liver	543
J13 Diagnostic percutaneous operations on liver	13,403
J14 Other puncture of liver	2,952
J16 Other operations on liver	41
J18 Excision of gall bladder	56,681
J19 Connection of gall bladder	51
J20 Repair of gall bladder	15
J21 Incision of gall bladder	239
J23 Other open operations on gall bladder	40
J24 Therapeutic percutaneous operations on gall bladder	236
J25 Diagnostic percutaneous operations on gall bladder	31
J26 Other operations on gall bladder	38
J27 Excision of bile duct	36
J28 Extirpation of lesion of bile duct	46
J29 Connection of hepatic duct	192
J30 Connection of common bile duct	161
J31 Open introduction of prosthesis into bile duct	49
J32 Repair of bile duct	69
J33 Incision of bile duct	200
J34 Plastic repair of sphincter of oddi using duodenal approach	51
J35 Incision of sphincter of oddi using duodenal approach	222
J36 Other operation on ampulla of vater using duodenal approach	36
J37 Other open operations on bile duct	139
J46 Therapeutic percutaneous attention to connection of bile duct	29
J47 Therapeutic percutaneous insertion of prosthesis into bile duct	1,056
J48 Other therapeutic percutaneous operations on bile duct	245
J49 Therapeutic operations on bile duct along t tube track	31
J50 Percutaneous examination of bile duct	683
J52 Other operations on bile duct	91
J55 Total excision of pancreas	53
J56 Excision of head of pancreas	913
J57 Other partial excision of pancreas	245
J58 Extirpation of lesion of pancreas	63
J59 Connection of pancreatic duct	67
J60 Other open operations on pancreatic duct	21
J61 Open drainage of lesion of pancreas	176
J62 Incision of pancreas	1
J63 Open examination of pancreas	6
J65 Other open operations on pancreas	299
J66 Therapeutic percutaneous operations on pancreas	323
J67 Diagnostic percutaneous operations on pancreas	324
J69 Total excision of spleen	1,351
J70 Other excision of spleen	39
J72 Other operations on spleen	151
M34 Total excision of bladder	1,696
M35 Partial excision of bladder	169
M36 Enlargement of bladder	258
M37 Other repair of bladder	231
M38 Open drainage of bladder	5,331
M39 Other open operations on contents of bladder	215
M41 Other open operations on bladder	118

M49 Other operations on bladder	34,041
T85 Block dissection of lymph nodes	3,744
T86 Sampling of lymph nodes	1,044
T87 Excision or biopsy of lymph node	14,176
T88 Drainage of lesion of lymph node	458
T89 Operations on lymphatic duct	16
T90 Contrast radiology of lymphatic tissue	10
T92 Other operations on lymphatic tissue	117
T94 Operations on branchial cleft	712
T96 Other operations on soft tissue	5,215
Total	395,084

General Endoscopy

The table below gives the HES codes that are assumed to be associated with medium risk general endoscopic operations.

HES Code	Number of Operations per Year
E48 Therapeutic fiberoptic endoscopic operations on lower respiratory tract	2,145
E49 Diagnostic fiberoptic endoscopic examination of lower respiratory tract	47,052
E62 Therapeutic endoscopic operations on mediastinum	13
E63 Diagnostic endoscopic examination of mediastinum	1,984
G43 Fiberoptic endoscopic extirpation of lesion of upper gastrointestinal tract	10,962
G44 Other fiberoptic therapeutic endoscopic operations on upper gastrointestinal tract	23,514
G45 Diagnostic fiberoptic endoscopic examination of upper gastrointestinal tract	492,141
G54 Therapeutic endoscopic operations on duodenum	319
G55 Diagnostic endoscopic examination of duodenum	463
G64 Therapeutic endoscopic operations on jejunum	284
G65 Diagnostic endoscopic examination of jejunum	63
G79 Therapeutic endoscopic operations on ileum	77
G80 Diagnostic endoscopic examination of ileum	590
H20 Endoscopic extirpation of lesion of colon	30,544
H22 Diagnostic endoscopic examination of colon	168,513
H23 Endoscopic extirpation of lesion of lower bowel using fiberoptic sigmoidoscope	12,469
H25 Diagnostic endoscopic examination of lower bowel using fiberoptic sigmoidoscope	135,078
J43 Diagnostic endoscopic retrograde examination of bile duct and pancreatic duct	11,660
J44 Diagnostic endoscopic retrograde examination of bile duct	823
Total	938,694

Anaesthetics

The table below gives the HES codes that are assumed to be associated with medium risk general anaesthetic procedures.

HES Code	Number of Operations per Year
F34 Excision of tonsil	58,111
F36 Other operations on tonsil	5,351
Total	63,462

Appendix 4: Summarising the known pessimistic and optimistic assumptions within the model

Some assumptions have been made that were known, or suspected, to be either pessimistic or optimistic. These are discussed within the text, but have been summarised here for ease of reference.

Pessimistic Assumptions.
That the residual mass on neurosurgical and posterior eye instruments was equal to that on tonsillectomy instruments (2.88mg) rather than general surgery instruments (1.26mg)
It is assumed that all instruments in a set come into contact with a patient and all obtain tissue mass
We have assumed that all medium risk titre is at a minimum of 4-log
We have assumed that all patients incubating CJD are infectious but will not exhibit clinical symptoms within the modelling period.
We have assumed that there is a linear relationship between ID50s and risk of infection, with 2 or more ID50s resulting in certain infection
We have assumed that there is no level of ID50s below which infection cannot occur.

Optimistic Assumptions.
That cross contamination of instruments does not occur.
That infection cannot take place without mass being transferred
That all the mass deposited on the inside of a neuroendoscope lumen is picked up by the next accessory to be passed down the lumen
That during the warm-up period, instruments that contact high-risk tissue in neurosurgery and posterior eye have been segregated from those that do not.
That any secondary infections in neurosurgery or posterior eye operations do not increase the prevalence of CJD in those patients undergoing neuroendoscopy, and vice versa.

Appendix 5: The age distribution of patients entering the model

The age distribution was estimated from the HES database which classifies patients into the following age bands: 0-14 years, 15 – 59 years, 60 – 74 years and 75 years and over. The summary figure of mean patient age is also provided by the HES data.

The methodology we used to fit a statistical distribution to the age data is subjective. Patient ages were assumed to be randomly assigned within their respective age-band, and a statistical distribution fitted to this using Statfit (©Simul8 Corporation). In cases where this approach was likely to be incorrect, manual adjustments were made to the ages and statistical distributions fitted to the modified data. An example of this is ENT where as the relative number of patients in the 0-14 year band is much greater than in the 60 years and over bands. Thus it seemed appropriate to ensure that the bulk of the patients in the 15- 59 year band were at the lower ages of this range and that the mean age was approximately correct.

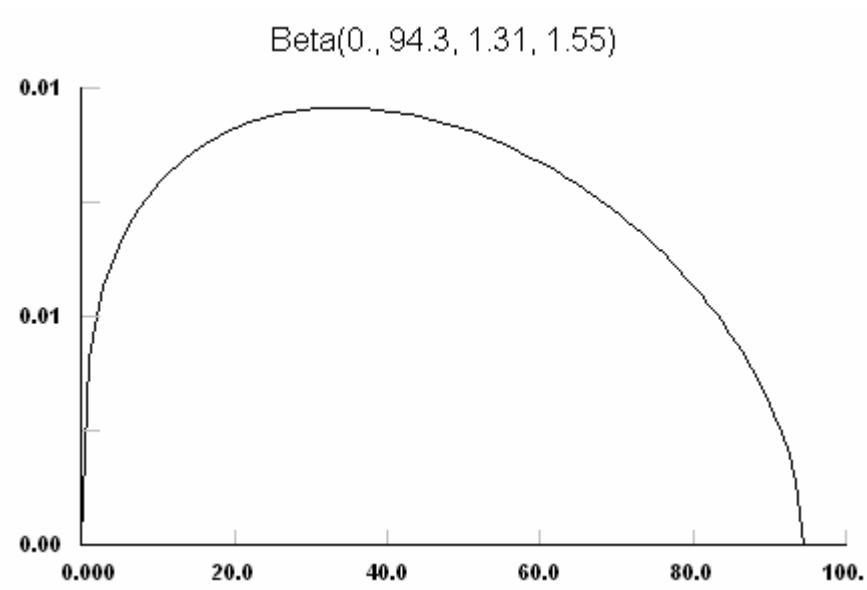
The following table gives the statistical approximations used within the model to simulate each patient's age:

Specialty	Statistical Fit of patient age
Brain	Beta : A1 = 1.306, A2 = 1.547 scaled to 0 – 94
Spinal cord	Beta : A1 = 1.390, A2 = 1.628 scaled to 0 - 94
Posterior Eye	Beta : A1 = 3.230, A2 = 1.870 scaled to 0 - 93
ENT / Anaesthetics	Pearson V : Alpha 2.896, Beta 38.282
Neuroendoscopy	Beta : A1 = 0.829, A2 = 1.689 scaled to 0 - 95
Anterior Eye	Weibull : Alpha 6.095, Beta 80.436
Maxillo-Facial	Triangular: Min 0, Max 95, Mode 0.460
General Surgery	Beta : A1 = 1.638, A2 = 1.353 scaled to 0 - 95
General Endoscopy	Triangular: Min 0, Max 95, Mode 75

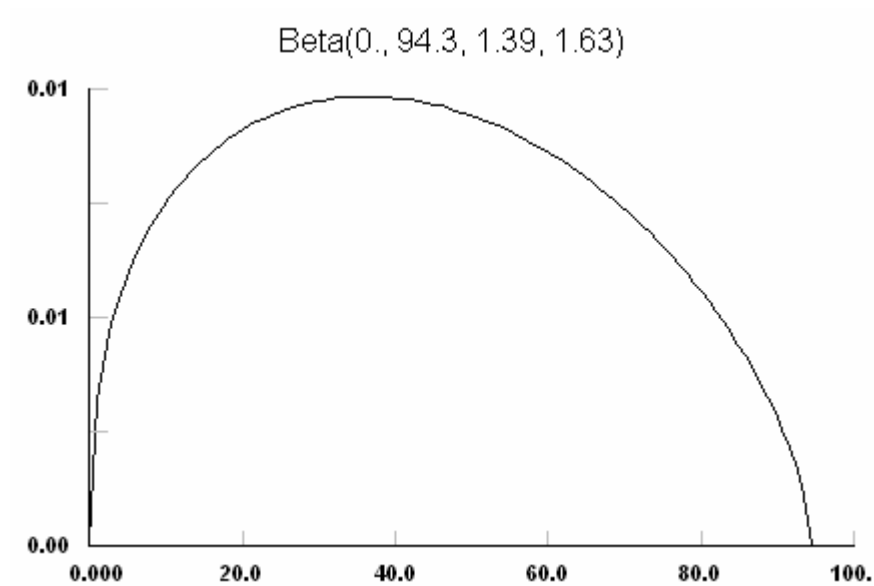
.Any age sampled as over 95 years was truncated to 95 years of age.

The distributions are represented graphically for ease of interpretation.

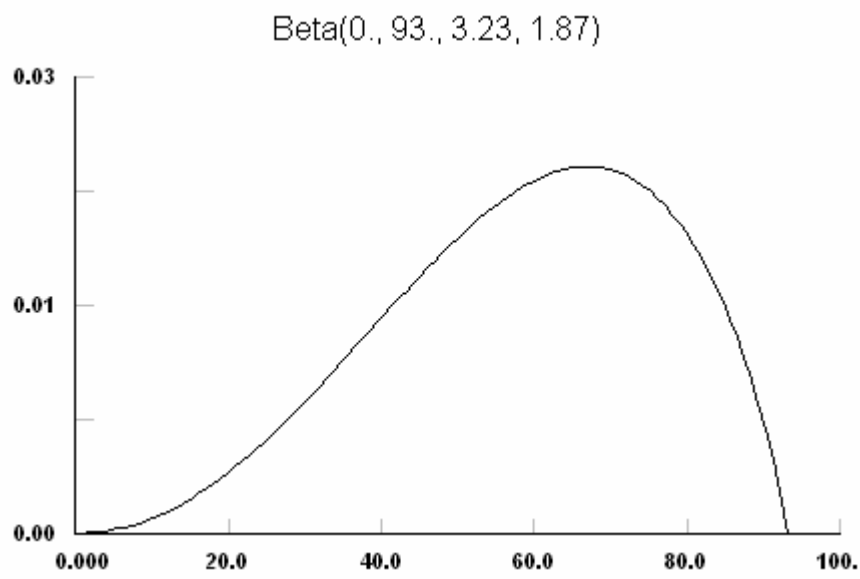
Assumed distribution of patients' ages for brain operations.



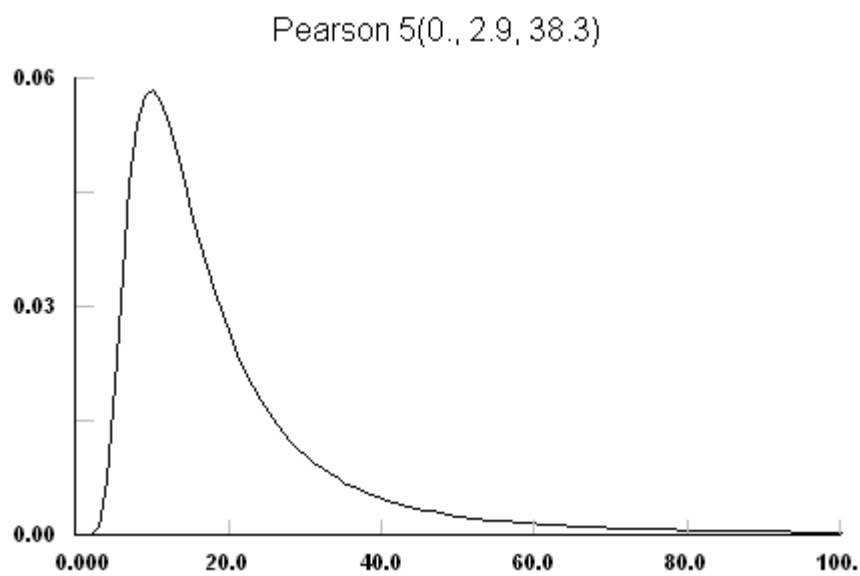
Assumed distribution of patients' ages for spinal cord operations.



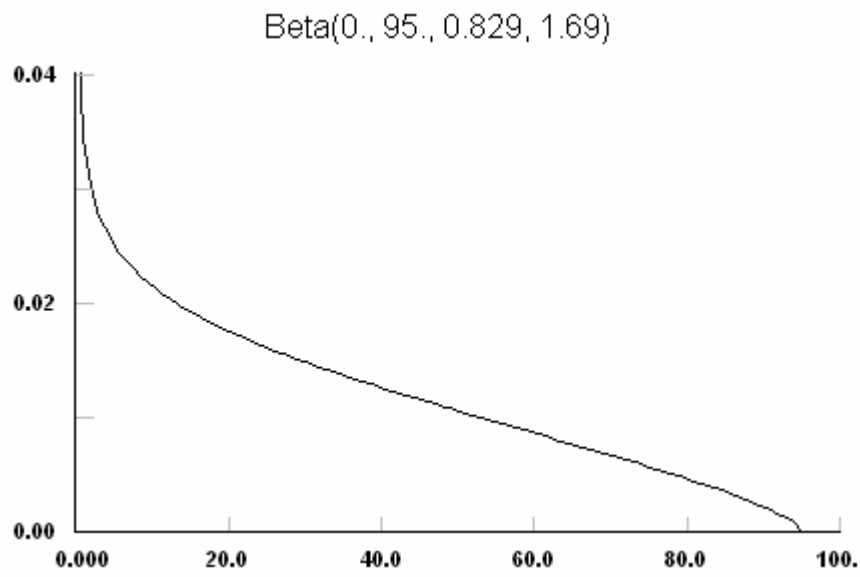
Assumed distribution of patients' ages for Posterior Eye operations



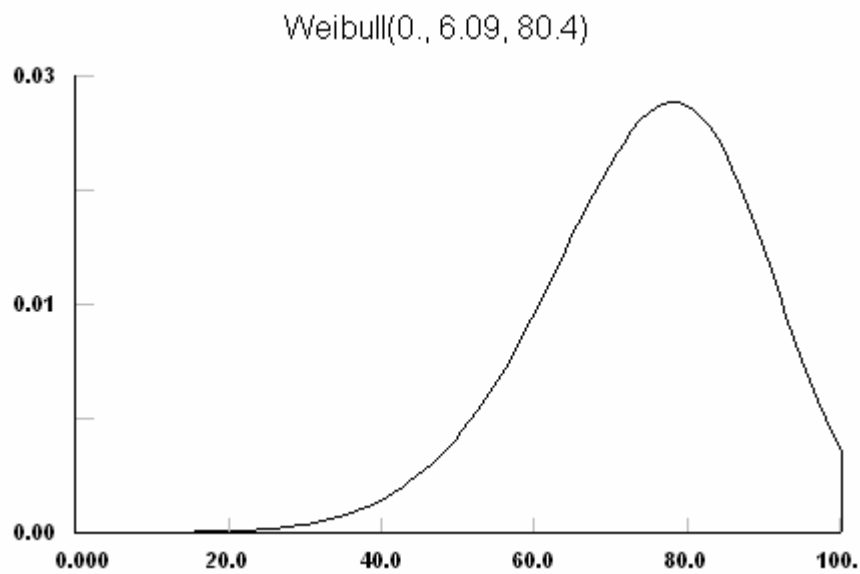
Assumed distribution of patients' ages for ENT / Anaesthetics operations.



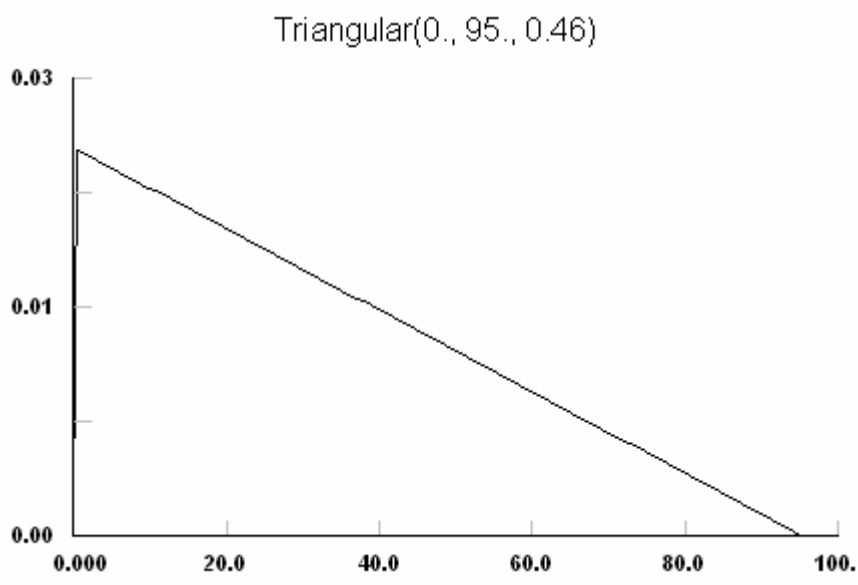
Assumed distribution of patients' ages for Neuroendoscopy.



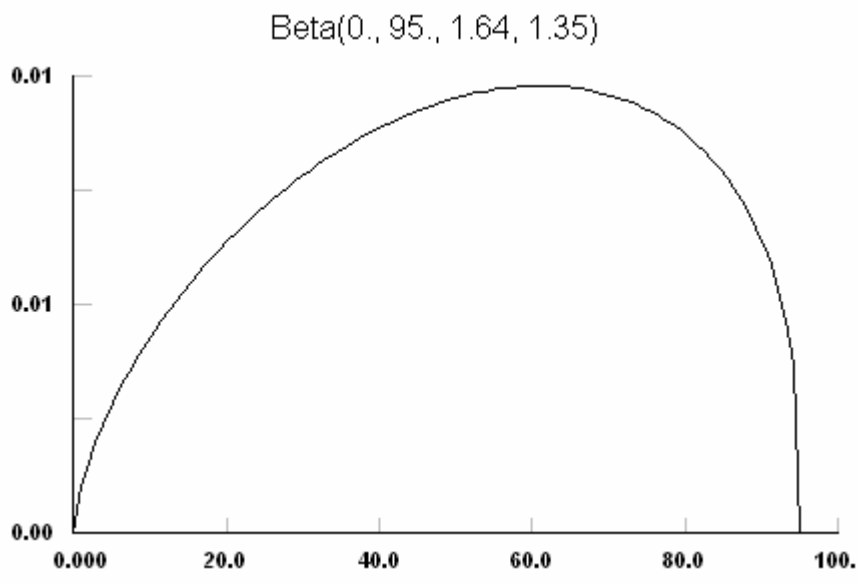
Assumed distribution of patients' ages for Anterior Eye operations.



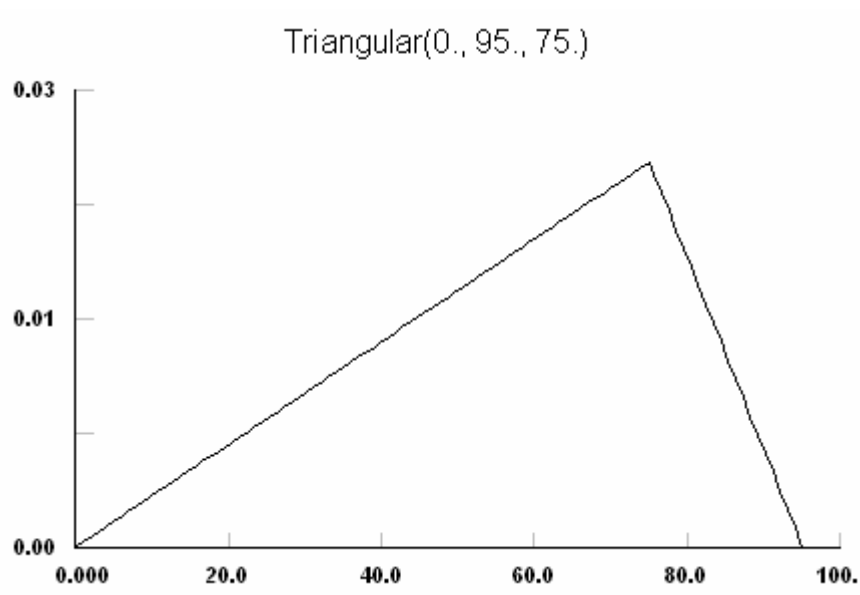
Assumed distribution of patients' ages for Maxillo-Facial operations.



Assumed distribution of patients' ages for General Surgery.



Assumed distribution of patients' ages for General Endoscopy.



Appendix 6: The return to surgery logic.

Methodology Description

Two potential methodologies are described that could be used for simulating the increased risks associated with further surgery. The first methodology is the most accurate, but requires significantly more computational time to produce results. A discussion on the methodologies and potential biases is given below.

1. Explicitly returning patients to surgery following an initial surgery.

This method would simulate the time of the initial operation and then subsequent operations (if any) for each patient within the 'geographical area'. Each patient would then have the initial and any second operations at defined time points, and where appropriate the times to the next operations would be re-sampled.

The resources required to structure the model in this manner would be extremely large, as all patients would need to be held within the model. Additionally data would be needed at an individual level on the probability of a return to surgery and where applicable the likely time distribution to surgery formulated. Given the difficulty we had in obtaining similar data at a much broader level, populating the model would rely on a number of assumptions.

2. Simulating return to surgery by adjusting the prevalence rates.

A less intensive computational approach is to simulate patients returning to surgery by increasing the prevalence of CJD within society. The magnitude of the increased risk is related to the relative risk of surgery given that a patient has a history of that surgery compared with a patient without such history that was estimated from HES data. The increase in prevalence is also related to the proportion of patients who have undergone surgery that have become infected.

This formula used within the model is

$$\frac{\text{Number of patients with primary infection} + \text{Number infectious via surgery} * \text{Return To Surgery value}}{\text{No of people} + \text{Number operated on} * \text{Return To Surgery value}}$$

As an example, consider a homogenous population of 100,000 people of which 10 are incubating CJD and are infectious, a return to surgery rate of 50, and just one surgical operation considered. At the model outset there is a 1/10,000 probability that the first operation would be on an infectious patient. If following 100 operations, 5 patients had become infected via surgery, the prevalence of CJD in those undergoing surgery would become.

$$(10 + 5*50) / (100,000 + 100*50) \text{ or } 260/105,000 \text{ or approximately } 1/400.$$

If however, in the first 100 operations no patients became infected, the prevalence of CJD in those undergoing surgery would decrease to

$10 / (100,000 + 100 * 50)$ or approximately 1/10,500 patients.

This methodology slightly underestimates the prevalence as the initial patient that provides the infection was inadvertently not included in the formulae, and this was discovered after the results were completed. Sensitivity analyses has shown this does not markedly effects the results.

In the previous report, the formula used for calculating the increased prevalence due to patients returning to surgery did not take into account those who had undergone surgery but had not become infected. This was noted and work on explicitly addressing this assumption was undertaken during the consultation period. The initial view was that correcting the formula would not markedly affect the results due to the large denominator (as approximately 2 million people were being analysed). However, since the prevalence of CJD is calculated for each age group, in the elderly the denominator was small and the omission of patients unaffected by previous surgery significantly over-estimated the prevalence of CJD. This in turn, over-estimated the probability of an operation being undertaken on an infectious patient. This correction to the formula has thus reduced the expected number of secondary infections.

Comparison of explicitly returning patients to surgery following an initial surgery and simulating return to surgery by adjusting the prevalence rates

The second method assumes that by increasing the prevalence of infectious patients a similar number of infectious cases will be produced as explicitly returning individual patients to surgery. However the numbers may not be exact, as these will vary due to the random numbers sampled.

As we have not constructed a model using methodology 1 the potential inaccuracy cannot be explicitly quantified, however the inaccuracy is likely to be small.

As such it is expected that the difference between the two methodologies is small, and the computational quicker version has been used due to the deadlines of the project.