Update Review: Risk of transmission via surgical interventional procedures of Creutzfeldt-Jakob disease (CJD)

1. Title of the project

Systematic review of Creutzfeldt-Jakob disease (CJD) risk via surgical interventional procedures and economic modelling of management policies

2. Name of project team and project lead

Project team:

School of Health and Related Research (ScHARR) - Technology Assessment Group, University of Sheffield.

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3. Background

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal disease affecting the brain. CJD is caused by an abnormal infectious protein called a prion. Once infected, the concentration of CJD prions varies throughout the body, but reaches high levels in the brain and posterior eye, resulting in symptoms such as rapidly progressive dementia, personality changes, and hallucinations. Most people with CJD will die within a year of the symptoms, usually from infection, as the condition also causes physical symptoms that leave the body vulnerable to infection.

Four classifications of CJD exist: sporadic CJD, variant CJD, familial CJD and iatrogenic CJD. Referrals of suspected CJD, and values for definitely-related CJD death (with neuropathological confirmation) or probably-related deaths (without neuropathological confirmation) are recorded by the CJD Research and Surveillance Unit in Edinburgh. [1] This source estimated that since 1990 there have been 3640 referrals and 2284 deaths of definite and probable CJD (data as at 2nd May 2017).

Sporadic CJD has historically been the most common type of CJD, and has accounted for around 100 deaths per year in the UK since 2010. The cause of sporadic CJD is uncertain.

Variant CJD (vCJD) was observed following the exposure of the UK population during the late 1980s and early 1990s to bovine spongiform encephalopathy that was transmitted to humans by eating food contaminated with the brain, spinal cord, or digestive tract of infected carcasses. This epidemic was first described in 1996[2] with the number of definitely or probably related deaths peaking at 28 in 2000. Since 2000, this value has diminished with only two definitely or probably related deaths reported since 2012. All people who have contracted vCJD have died.

Familial (or genetic CJD) accounts for approximately 10 definite or probably related deaths per year. The number of definite or probably related iatrogenic deaths, which are caused by medical or surgical treatment, are fewer still, with none believed to have been through a surgical route, with the majority associated with blood transfusion.

Prions are unlikely to be completely deactivated by conventional hospital cleansing and sterilisation techniques. Patients may therefore be infected iatrogenically with CJD by surgical instruments, endoscopes or laryngoscopes used previously in patients who have asymptomatic CJD but who are infectious.

Immediately following the outbreak, the potential scale of the vCJD infection remained uncertain and estimations varied.[3-5] Surgical transmission of CJD was considered to pose a potential risk to public health. Therefore, in 2005 the National Institute for Health and Care Excellence (NICE) commissioned ScHARR, at the University of Sheffield to conduct a systematic review and cost-effectiveness model of evidence on patient safety and reduction of risks of transmission of CJD.[6] This evidence, together with data collected from elicitation experts were used to populate a model assessing the cost-effectiveness of single-use surgical instruments.[7, 8] The outputs from the model were used to inform the guidance produced by the NICE IP Programme "*Patient safety and reduction of risks of transmission of Creutzfeldt-Jakob Disease (CJD) and vCJD*" (IPG196). While the cost-effectiveness analysis indicated that the introduction of single-use instruments was not cost-effective, there was great uncertainty in these results and a recommendation was made by the study authors that policy might need to be revised if pertinent data become available.

An epidemic of CJD has not occurred since the original guidance and there is no evidence of transmission by surgery to date. However, a number of developments are believed to have occurred since 2006, which may be relevant to the research update. These include:

- the finding of abnormal prion accumulation in the appendices of low-risk cohorts [e.g. born after 1996],
- continued evolution of high quality and less expensive single-use instruments,
- the failure of new decontamination methods effective against human prions to appear; the experts consulted for IPG196 believed these would emerge within five years,
- difficulties implementing the recommendations in IPG196 across a number of units.

The Medical Director of NHS England, the Chief Medical Officer and the chair of the DH Advisory Committee on Dangerous Pathogens (ACDP) have indicated that a full update of IPG196 is needed to have a system in place that is fit for purpose and to reduce the risks of horizontal transmission of CJD.

In 2017, the NICE Interventional Procedures Programme commissioned ScHARR to update the clinical and cost-effectiveness evidence from 2005 (project no. IP1553).

4. Decision Problem

Purpose of the decision to be made

The objective of the proposed work is to review the evidence base for the current risk of CJD transmission related to surgery in order to provide up-to-date relevant evidence to NICE about the cost-effectiveness of potential management strategies.

Review question

What is the current relevant evidence (since the last review in 2005) about the risk of CJD transmission during surgical procedures and what is the cost-effectiveness of management strategies to reduce the risk of CJD transmission during surgical procedures.

Research objectives

1. To update the systematic reviews of clinical evidence on patient safety and reduction of risks of transmission of CJD
2. To undertake mathematical modelling taking into account advice from the committee and NICE. The distributions elicited in the original research will be used alongside Bayesian Inference techniques to allow the modelled estimates to be aligned with observed cases of CJD
3. To produce a 'final report' summarising the available evidence, the modelling undertaken and the cost-effectiveness results

5. Research Methods

Focussing the review questions from 2005 vCJD review to be relevant today

The original research project conducted by ScHARR in 2005 comprised a series of systematic reviews. These were:

1. *The UK incidence and prevalence of CJD and vCJD*
2. *The secondary transmission of CJD by invasive diagnostic, surgical or dental procedures (by type of procedure)*
3. *The incubation period of acquired human transmissible spongiform encephalopathies (TSEs)*
4. *The likely infectivity of infectious tissue and the infectious mass required to transmit CJD/vCJD*

5. *The decontamination of surgical, anaesthetic and diagnostic instruments, scopes and implantable devices (by type of procedure)*
6. *The extent to which surgical instruments remain in their original sets following use and decontamination*
7. *The complication rates associated with the use of single-use vs reusable anaesthetic, surgical or diagnostic instruments (by type of procedure)*
8. *The risk of future surgery following surgery*

The objective of the current research is to update the evidence from the previous research project to be relevant for the CJD decision problem in 2017. This protocol is being developed in consultation with the NICE IPAC Committee to update relevant research questions and include:

1. What is the incidence of CJD and what is the prevalence of CJD-related prions in humans in the UK?
2. What is the risk of secondary transmission of CJD by surgical procedure?
3. What are the incubation periods of acquired TSEs?
4. What is the infectivity of CJD?
5. What is the evidence on the efficacy of decontamination of instruments with CJD/TSE/prions?
6. What is the evidence that instruments used for high-risk procedures remain in their original sets?
7. What is the evidence for complication rates of single-use compared with reusable instruments for high-risk procedures?
8. What is the evidence for risk of future surgery for a patient undergoing high-risk procedures?

We intend to update the evidence for the review questions in the 2005 research project using best practice systematic review methodology according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009)[9] standards and will register the protocol on the PROSPERO systematic review database. These methods will also be supplemented by the historical expert elicitation exercises.

The inclusion criteria will differ for different questions, but might be broadly summarised in Table 1.

Table 1: Eligibility criteria

Population	People at risk of CJD transmission via surgery
Intervention	Management strategies to reduce the risk of transmission of CJD during surgery. High risk procedures are those defined by NICE interventional procedure guidance 196. Patient safety and reduction of risk of transmission of Creutzfeldt–Jakob disease (CJD) via interventional procedures. Appendix C. NICE; 2008. Available from:

	https://www.nice.org.uk/guidance/ipg196/documents/ipg196-patient-safety-and-reduction-of-risk-of-transmission-of-creutzfeldtjakob-disease-cjd-via-interventional-procedures-guidance2 (Accessed 27 July 2017).
Comparator	No intervention or appropriate control
Outcomes	Incidence and prevalence of CJD Prevalence of the presence of prion in tissue Risk of transmission of CJD Clinical effectiveness of management strategies for reducing risk of CJD Cost-effectiveness of management strategies
Setting	Any setting relevant to UK clinical practice. The majority of evidence is likely to relate to secondary care
Studies	Study designs permitted for inclusion will be considered separately for each review question. Included studies will be restricted to those published in the English language.

Search strategy

Information sources

In the original research conducted in 2005, each of the systematic reviews were conducted using individual search strategies. All searches were conducted between January and June in 2005 12 bibliographic databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), Science Citation Index, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment Database (NHS HTA), CINAHL, AMED, BIOSIS, Health Economic Evaluations Database (HEED)

In the current research, we propose to conduct the searches in three instead of 12 databases including:

- MEDLINE (Ovid)
- EMBASE (Ovid)
- Science Citation Index (Web of Science)

As evidence relevant to one question was often only found in the citations retrieved by searches conducted for another question in the 2005 reviews, the proposed searches will combine terms that are relevant for more than one question. Five targeted searches, instead of eight, for reviews 1-8 will be conducted which combine:

i. Reviews 1 and 3
ii. Reviews 2, 4 and 5
iii. Review 6
iv. Review 7
v. Review 8

The update searches will be conducted to retrieve evidence from 2005 to present. Keywords will be reviewed and clinical advice will be sought to ensure that where necessary, synonyms or additional terms will be added or amended. Supplementary citation searches of certain relevant included studies from the original review will also be conducted.

A targeted search strategy to retrieve evidence to inform the cost-effectiveness modelling will also be conducted in MEDLINE, EMBASE, Web of Science, CDSR (Cochrane Library), HTA (Cochrane Library), and NHS EED (Cochrane Library) from 2004 to present. The proposed searches are outlined in the Appendix. Where necessary, data will be sought and incorporated that are not captured by the literature searches. These data are likely to include the costs of single-use instruments and the level of compliance with previous guidance undertaken by decontamination services.

Study selection

Results from the electronic bibliographic searches will be imported into reference management software, EndNote (version 8, Thompson Reuters), and duplicates removed. Titles and abstracts of retrieved records will be examined by one reviewer (LU) and irrelevant citations excluded. A proportion (10%) of randomly selected excluded citations will be double-checked by a second reviewer (CC). All full text articles will be independently assessed for inclusion by two reviewers (LU, CC). Any disagreements will be resolved by discussion, with involvement of a third team member (MS) if required. Data on the incidence of CJD identified from countries outside of the UK will be incorporated narratively if deemed relevant.

Literature identified within the cost-effectiveness review would be processed in a similar manner. Titles and abstracts of retrieved records will be examined by one reviewer (MS) and irrelevant citations excluded. A proportion (10%) of randomly selected excluded citations will be double-checked by a second reviewer (LU). All full text articles will be independently assessed for inclusion by two reviewers (MS, LU). Any disagreements will be resolved by discussion, with involvement of a third team member (CC) if required.

Data extraction

Bespoke data extraction forms will be developed for each review question to ensure relevant outcome data for each review question are captured. All data will be extracted by one systematic reviewer (LU) and independently checked by a second reviewer (CC). Discrepancies will be resolved by discussion, with reference to a third team member if necessary.

Quality assessment

Studies will be assessed by validated quality assessment tools that are appropriate for each study design in question e.g., Cochrane Risk of Bias or Critical Appraisal Skills Programme (CASP) tools. Tools will be modified where necessary to appraise only and all relevant quality

criteria for each review question. For each review question, two reviewers (LU, CC) will independently assess the risk of bias in included studies against the appropriate quality assessment tool.

Data analysis / synthesis

Data will be tabulated, synthesised and discussed narratively in the submitted report for each review question. Where appropriate, meta-analyses will be conducted by an experienced statistician using appropriate software and heterogeneity will be explored using meta-regression. Subgroup analyses will be considered where recommended by clinical advice (e.g. by type of surgery).

Meta-bias(es)

The review will include an examination of external validity to address how well the studies retrieved match the original research question and to identify gaps in the evidence base.

6. Cost-effectiveness analysis

The intention is to use the model structure developed in the modelling undertaken for IPG196. This model structure has been published.[7] Whether all the surgical sites evaluated in the original report for NICE[8] will be maintained or whether only those deemed to be at highest risk of infectivity (brain and posterior eye)[10] will be included will be decided in consultation with the committee. Discussions on whether the assumptions that patients born after 1996 would not have vCJD should be relaxed will be held with NICE.

The analyses will still start in 2005 in order that the model can compare the number of surgical CJD infections with those that have been observed in the interim period. It is anticipated that the model will be run using the data using the original elicited distributions, alongside Bayesian inference. Following the results of probabilistic sensitivity analyses, each iteration will be given a weight based on how closely the estimated data fitted that observed since 2005, thus penalising parameter configurations that do not align with observed data. Data provided from the systematic review will also be incorporated where appropriate. Care will be taken to replicate the conditions that were prevalent during the period where data were observed, for example if measures to protect set integrity have not been enforced then this would be reflected within the modelling. We will work closely with the Appraisal Committee to ensure that the historical elicited ranges in the parameters are not overly precise which could hinder the Bayesian inference. If this is shown to be the case then further elicitation sessions may be necessary.

The model will be run evaluating different strategies for preventing the iatrogenic spread of CJD ranging from complete use of single use instruments to not making changes to the current system. Further strategies will be determined in discussion with the committee. It is noted that the recommendations in IPG196 have proven difficult to enforce, particularly in relation to

preserving the integrity of sets and that this will be included in the modelling if appropriate and possible.

The time horizon for the model will be determined in discussion with the committee in order to find an acceptable balance between the usefulness of results to the committee and the computational time required to generate the results. In the original work, it was believed that a decontaminant that would deactivate CJD prions would be in place by 2010; however, this did not materialise.

The output from the model will be the costs and quality adjusted life years (QALYs) associated with each strategy (both current practice and alternative strategies). A full incremental analysis will be undertaken including all strategies evaluated to determine the strategy that is expected to be cost-effective using thresholds currently recommended by NICE (£20,000 - £30,0000 per QALY gained).[11]

7. Dissemination

A final report including the background, methods, results and discussion of the clinical and cost-effectiveness evidence will be produced and submitted to the research commissioners. In addition, and following submission of the full report, the findings will be made available in relevant high quality peer reviewed journal publications.

8. Team expertise

Matt Stevenson (Professor of Health Technology Assessment) is a mathematical modeller and Technical Director of ScHARR-TAG, a member of NICE Appraisal Committee C and has published in excess of 70 peer-reviewed papers. Matt led the work conducted by ScHARR that informed IPG196.

Lesley Uttley (Research Fellow in Systematic Review) has extensive experience in undertaking systematic reviews of clinical effectiveness evidence for health technologies, and appraising evidence submissions such as NICE single technology appraisals.

Christopher Carroll (Reader in Systematic Review and Evidence Synthesis) has extensive experience in undertaking systematic reviews of clinical effectiveness evidence for health technologies, and appraising evidence submissions such as NICE single technology appraisals.

John Stevens (Reader in Decision Science) has extensive experience in Bayesian statistics and evidence synthesis.

Ruth Wong (Information Specialist) has extensive experience of undertaking and appraising literature searches for ScHARR-TAG and other external projects.

Jeremy Oakley (Professor of Statistics) has extensive experience in Bayesian statistics, in particular eliciting probability distributions and analysing uncertainty in complex computer models. He was a collaborator on the modelling work conducted by ScHARR that informed IPG196.

Stephen Chick (Professor of Technology and Operations Management, Professor of Healthcare Management – INSEAD, France) has extensive experience in simulation modelling. He was a collaborator on the modelling work conducted by ScHARR that informed IPG196.

9. Competing interests of authors

ScHARR authors: none

Sponsor: Funding for this work was provided by the NICE IP Programme [IP1553], UK. The funders were involved in developing the protocol but will have no role in data analyses or interpretation.

10. Timetable of work

Milestone	
Final protocol	31st August 2017
Systematic review draft report including key changes in evidence summary	31st January 2017
Draft assessment report	30th April 2018
Final assessment report	31st May 2018

11. References

1. Edinburgh TUo. THE NATIONAL CJD RESEARCH & SURVEILLANCE UNIT (NCJDRSU). 2017. http://www.cjd.ed.ac.uk/ (Accessed 11.07.2017).
2. Will RG, Ironside J, Zeidler M, Estibeiro K, Cousens S, Smith P, *et al.* A new variant of Creutzfeldt-Jakob disease in the UK. *The Lancet* 1996;347:921-5.
3. Hilton DA, Ghani AC, Conyers L, Edwards P, McCardle L, Ritchie D, *et al.* Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *The Journal of pathology* 2004;203:733-9.
4. Ghani AC, Ferguson NM, Donnelly CA, Anderson RM. Factors determining the pattern of the variant Creutzfeldt-Jakob disease (vCJD) epidemic in the UK. *Proceedings of the Royal Society of London B: Biological Sciences* 2003;270:689-98.
5. Clarke P, Ghani AC. Projections of the future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility. *Journal of the Royal Society Interface* 2005;2:19-31.
6. Lloyd Jones M, Stevenson M, Sutton A. Patient safety and reduction of risk of transmission of Creutzfeldt– Jakob disease (CJD) via interventional procedures. Systematic literature reviews final report. National Institute for Health and Care Excellence: School of Health and Related Research, University of Sheffield; 2006.
7. Stevenson M, Oakley JE, Chick SE, Chalkidou K. The cost-effectiveness of surgical instrument management policies to reduce the risk of vCJD transmission to humans. *Journal of the Operational Research Society* 2009;60:506-18.
8. Stevenson M, Oakley J, Chick SE. Patient safety and reduction of risk of transmission of Creutzfeldt–Jakob disease (CJD) via interventional procedures—final report: School of Health and Related Research, University of Sheffield; 2006.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009;6:e1000097.
10. Bruce M, McConnell I, Will R, Ironside J. Detection of variant Creutzfeldt-Jakob disease infectivity in extraneural tissues. *The Lancet* 2001;358:208-9.
11. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal; 2013.

Appendix:

Search strategies

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE®

Reviews 1 & 3: The UK incidence and prevalence of CJD and the incubation period of acquired human TSES

Key terms for 'incidence and prevalence' or 'incubation' (10-15) are combined with 'CJD' population terms (1-9). To apply date restriction from 2005 to present.

1 exp Creutzfeldt-Jakob Syndrome/
2 ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw.
3 (cjd or vcjd or v-cjd).tw.
4 exp Prion Diseases/
5 exp Prions/
6 ((transmissible or spong*) adj encephalopath*).tw.
7 (prion* or tse).tw.
8 prp.tw.
9 or/1-8
10 exp Incidence/
11 exp Prevalence/
12 incidence.tw.
13 prevalence.tw.
14 or/10-13
15 incubat*.tw.
16 9 and (14 or 15)
17 limit 16 to yr="2005 -Current"

Reviews 2, 4 & 5: The secondary transmission of CJD by invasive diagnostic or surgical procedures; Infectious mass required to transmit CJD; and the decontamination of surgical, anaesthetic and diagnostic instruments, scopes and implantable devices

Key terms for 'transmission', 'transfer' and 'instrument decontamination' (10-16) are combined with 'CJD' population terms (1-9). To apply date restriction from 2005 to present.

1 exp Creutzfeldt-Jakob Syndrome/
2 ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw.
3 (cjd or vcjd or v-cjd).tw.
4 exp Prion Diseases/
5 exp Prions/
6 ((transmissible or spong*) adj encephalopath*).tw.
7 (prion* or tse).tw.
8 prp.tw.
9 or/1-8
10 ((transmission or transmit* or iatrogenic or transfer*) adj5 (creutzfeldt or cjd or vcjd or v-cjd or encephalopath* or prion* or tse or prp)).tw.
11 exp Surgical instruments/
12 exp Decontamination/
13 exp Sterilization/
14 11 and (12 or 13)

15 ((surgery or surgical* or instrument* or device* or equipment*) adj5 (decontaminat* or reprocess* or disinfect* or wash* or clean* or steril* or contaminat* or prerinse or pre-rinse or inactivat*)).tw.
16 14 or 15
17 9 and (10 or 16)
18 limit 17 to yr="2005 -Current"

Review 6: The extent to which surgical instruments remain in their original sets following use and decontamination

Key terms for 'instrument decontamination' (1-6) are combined with 'high-risk surgical procedures' (7-22). High-risk surgery terms developed from NICE's IPG 196 guidance (https://www.nice.org.uk/guidance/ipg196/documents/ipg196-patient-safety-and-reduction-of-risk-of-transmission-of-creutzfeldtjakob-disease-cjd-via-interventional-procedures-guidance2). To apply date restriction from 2005 to present.

1 exp Surgical Instruments/
2 exp Decontamination/
3 exp Sterilization/
4 1 and (2 or 3)
5 ((surgery or surgical* or instrument* or device* or equipment*) adj5 (decontaminat* or reprocess* or disinfect* or wash* or clean* or steril* or contaminat* or prerinse or pre-rinse or inactivat*)).tw.
6 4 or 5
7 Neurosurgery/
8 Neurosurgical Procedures/
9 (neurosurgery or neurological surgery).tw.
10 exp Brain/su [Surgery]
11 exp Meninges/su [Surgery]
12 exp Pituitary Gland/su [Surgery]
13 Pineal Gland/su [Surgery]
14 ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical* or excision or lesion or ablation or operation* or neurostimulation or connection or destruction)).tw.
15 exp Cranial Nerves/su [Surgery]
16 ((cranial or dura) adj5 (graft* or transection or destruction or lesion or repair* or decompress* or neurostimulation or exploration or operation*)).tw.
17 Ophthalmologic Surgical Procedures/
18 ((eye or vitreous or retina) adj5 (surgery or surgical* or excision or operation* or photocoagulation or destruction)).tw.
19 Eye/su [Surgery]
20 Vitreous Body/su [Surgery]
21 exp Retina/su [Surgery]
22 or/7-21
23 6 and 22
24 limit 23 to yr="2005 -Current"

Review 7: The complication rates associated with the use of single-use vs reusable anaesthetic, diagnostic or surgical instruments

Key terms for 'disposable or single use' instruments (1-5) combined with 'high-risk surgical procedures' (6-21) and 'complications' (22-26). To apply date restriction from 2005 to present.

1 (disposable or dispose* or nondispos* or non-dispos* or reus* or re-us* or "single use" or "single-use").mp.
2 Disposable Equipment/
3 exp Equipment Reuse/
4 (ultrasonic aspirator or aneurysm clip applicator or rhoton dissectors or microsurgical scissors or upcut rongeurs or budde halo or retraction system or self-retaining retractors or neuroendoscope*).mp.
5 or/1-4
6 Neurosurgery/
7 Neurosurgical Procedures/
8 (neurosurgery or neurological surgery).tw.
9 exp Brain/su [Surgery]
10 exp Meninges/su [Surgery]
11 exp Pituitary Gland/su [Surgery]
12 Pineal Gland/su [Surgery]
13 ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical* or excision or lesion or ablation or operation* or neurostimulation or connection or destruction)).tw.
14 exp Cranial Nerves/su [Surgery]
15 ((cranial or dura) adj5 (graft* or transection or destruction or lesion or repair* or decompress* or neurostimulation or exploration or operation*)).tw.
16 Ophthalmologic Surgical Procedures/
17 ((eye or vitreous or retina) adj5 (surgery or surgical* or excision or operation* or photocoagulation or destruction)).tw.
18 Eye/su [Surgery]
19 Vitreous Body/su [Surgery]
20 exp Retina/su [Surgery]
21 or/6-20
22 complication*.mp.
23 co.fs.
24 exp Postoperative Complications/
25 exp Intraoperative Complications/
26 or/22-25
27 5 and 21 and 26
28 limit 27 to yr="2005 -Current"

Review 8: The risk of future surgery following surgery

Key terms for ‘reoperation’ or ‘repeat surgery’ combined (1-4) with ‘high-risk surgical procedures’ (5-20). No date restrictions to be applied.

1 *Reoperation/
2 reoperat*.tw.
3 ((repeat or revision) adj3 (surgery or surgical* or operat*)).tw.
4 or/1-3
5 Neurosurgery/
6 Neurosurgical Procedures/
7 (neurosurgery or neurological surgery).tw.
8 exp Brain/su [Surgery]
9 exp Meninges/su [Surgery]
10 exp Pituitary Gland/su [Surgery]
11 Pineal Gland/su [Surgery]

12 ((brain or meninges or cerebral or pituitary or pineal) adj5 (surgery or surgical* or excision or lesion or ablation or operation* or neurostimulation or connection or destruction)).tw.
13 exp Cranial Nerves/su [Surgery]
14 ((cranial or dura) adj5 (graft* or transection or destruction or lesion or repair* or decompress* or neurostimulation or exploration or operation*)).tw.
15 Ophthalmologic Surgical Procedures/
16 ((eye or vitreous or retina) adj5 (surgery or surgical* or excision or operation* or photocoagulation or destruction)).tw.
17 Eye/su [Surgery]
18 Vitreous Body/su [Surgery]
19 exp Retina/su [Surgery]
20 or/5-19
21 4 and 20

Cost-effectiveness review

Key terms for 'CJD' (1-9) combined with an economics search filter (10-31). To apply date restriction from 2004 to present.

1 exp Creutzfeldt-Jakob Syndrome/
2 ((creutzfeldt jakob or creutzfeldt-jakob) adj (disease or syndrome)).tw.
3 (cjd or vcjd or v-cjd).tw.
4 exp Prion Diseases/
5 exp PRIONS/
6 ((transmissible or spong*) adj encephalopath*).tw.
7 (prion* or tse).tw.
8 prp.tw.
9 or/1-8
10 exp "Costs and Cost Analysis"/
11 Economics/
12 exp Economics, Hospital/
13 exp Economics, Medical/
14 Economics, Nursing/
15 exp models, economic/
16 Economics, Pharmaceutical/
17 exp "Fees and Charges"/
18 exp Budgets/
19 budget$.tw.
20 ec.fs.
21 cost$.ti.
22 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
23 (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
24 (price$ or pricing$).tw.
25 (financial or finance or finances or financed).tw.
26 (fee or fees).tw.
27 (value adj2 (money or monetary)).tw.
28 quality-adjusted life years/
29 (qaly or qalys).af.
30 (quality adjusted life year or quality adjusted life years).af.
31 or/10-30
32 9 and 31
33 limit 32 to yr="2004 -Current"