CJD INCIDENTS PANEL

Management of possible exposure to CJD through medical procedures

Framework Document

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Foreword

The CJD Incidents Panel is the expert committee set up by the Department of Health to advise all those bodies responsible for the provision and delivery of health care on the most appropriate action to take to handle incidents involving potential transmission of Creutzfeldt-Jakob Disease (CJD) between patients through clinical interventions, including via surgical instruments, tissues, organs and blood. This document explains the basis on which the Panel provides advice and sets out the reasoning behind the Incidents Panel's advice. It is intended to support health care professionals and managers involved in incidents.

Creutzfeldt-Jakob Disease (CJD) and related human transmissible spongiform encephalopathies (TSEs) are rare and fatal neurodegenerative diseases occurring throughout the world. In the majority of cases the disease occurs randomly with no identifiable cause. A few cases are associated with gene mutation and are termed "familial" and a very small number have been accidentally transmitted from person to person as a result of medical procedures. In March 1996 a previously unrecognised form of the disease was identified, now known as variant CJD (vCJD). The most likely explanation of vCJD cases to date is exposure to the agent that causes Bovine Spongiform Encephalopathy (BSE).

This document sets out proposals for managing incidents involving possible exposure to TSE agent in healthcare settings. Incidents arise when patients who are diagnosed or suspected of having TSE are found to have undergone a medical procedure at some time in the past. Other patients could be put at risk if the TSE agent is transmitted through contaminated instruments and/or devices, or donated blood or other tissues or organs.

This framework document has been considered by the Chief Medical Officers for the UK. While they supported most of the proposals within this paper, they have not yet decided on the proposal to establish a confidential database without consent. The Chief Medical Officers have asked that the sections of the document that relate to the database are 'greyed out' for the time being.

The risk of transmitting TSEs through medical interventions is not fully understood, and this document has been prepared in the face of great scientific uncertainty. While there are many areas of doubt, this guidance has been able to draw on the work of the Spongiform Encephalopathy Advisory Committee (SEAC), the government's expert scientific committee on TSEs.

The document particularly draws on two reports: 'Risk Assessment for Transmission of variant CJD via Surgical Instruments: A modelling approach and numerical scenarios'[1] (referred to in this document as the surgical risk assessment), and 'Assessment of the risk of exposure to variant CJD infectivity in blood and blood products'[2] (referred to in this document as the blood risk assessment). The document also builds on the conclusions of an expert Peer Review Group that was set up by SEAC to assess the available data in this area.

This is a working document and will be updated as new scientific evidence becomes available. It currently covers incidents involving medical interventions and blood donations. The section on managing blood incidents has been 'greyed out' as it has not yet been finalised. Future versions will also address tissue and organ donations and transplantation.

The document is available to the medical and allied professions and to anyone else with an interest. It is available on the Department of Health's website at:

http://www.doh.gov.uk/cjd/incidentspanel

Executive summary

Although the evidence remains incomplete, scientific opinion suggests that it is possible that TSEs may be transmitted via surgical instruments used on patients incubating the disease, or in blood or other tissues or organs donated by individuals incubating the disease. These risks are unknown and current procedures for decontaminating surgical instruments between uses cannot be guaranteed to eliminate the abnormal prion proteins that are thought to be responsible for the transmission of TSEs. In addition, while there is evidence that sporadic CJD is not transmitted in blood, less is known about variant CJD. Therefore transmission of variant CJD in blood cannot be ruled out.

Public health actions are needed as contaminated surgical instruments and blood may transmit TSEs to other patients.

The document is intended for the whole of the UK and the Department of Health has set up an expert group to advise all those bodies responsible for the provision and delivery of health care on the most appropriate action to take to handle incidents involving potential transmission of Creutzfeldt-Jakob Disease (CJD) between patients through clinical interventions, including via surgical instruments, tissues, organs or blood.

This expert group, the CJD Incidents Panel includes ethicists, lay members, and scientific and medical experts. This document sets out a proposed framework for the Panel's advice and will also inform health professionals and managers involved in these incidents.

There is a great deal of scientific uncertainty about the infectivity of different tissues (including blood) in people incubating TSEs and about the effectiveness of reducing infectivity by decontaminating surgical instruments and of processing blood. This document sets out what is known about these factors, and shows how the Panel assesses the risk for different medical procedures.

The document also advises on identifying, investigating and managing these incidents. The Panel proposes four main courses of action:

Removing the instruments/blood products from use

This protects public health while the risks are being assessed. The Panel may advise that instruments are permanently removed from use or that they are unlikely to pose a risk to the public and may be returned to use. The Panel will also advise on the removal from use of blood or plasma products donated by people who later develop TSEs.

Setting up a confidential database of all possibly exposed people

The database would be used for public health research and for the long-term follow up of individuals who could have been exposed to CJD through medical procedures. This database would be used to find out whether any exposed individuals go on to develop TSEs themselves, so increasing our knowledge of these risks.

There is a strong argument that people should be able to choose whether or not they are told about their possible exposure. To enable this choice, it is proposed that possibly exposed people are not asked for their consent before being recorded on this register. This is because being asked for their consent would remove the choice of not being told about their exposure. Instead it is proposed that individuals who wish to know if they are on the database, and the details and significance of their exposure, should be able, after appropriate counselling, to obtain the information. Under the circumstances it is more appropriate to advertise the existence of the database through a communication strategy and to give individuals the option to opt out of the database and/or to discover the nature of the data held.

The database will NOT:

- Be used to check whether an individual presenting for surgery, blood, organ or tissue donation has been potentially exposed;
- Be available to any person except:

  those responsible for running the database

  those analysing the database to determine the risk of developing TSEs

  the individual who will have access to their own data, with the appropriate controls to secure confidentiality,

It is proposed that most people would not be informed about their possible exposure. This is because the average incubation period for TSEs transmitted between people by medical procedures is unknown but could be well over 10 years; there is currently no reliable diagnostic test for people incubating the disease; there is no cure for this fatal disease; and the risks of transmitting TSEs through medical procedures are very uncertain. Moreover, TSEs are not thought to spread between people through normal social contact. Therefore, learning about one's exposure would be of doubtful benefit to individuals and could inflict psychological harm.

The Panel has considered carefully the sensitive issues surrounding these proposals and has concluded that there are very strong reasons for the establishment of a database of potentially exposed individuals. The issue of consent is controversial but the Panel considers this to be a very special case, as so little is known about the disease and the interval between exposure and disease may be very long. Individuals have a right to decide whether their personal information is kept on this database and to exercise the right to remove their details without necessarily finding out about potential exposure.

Informing some individuals about their exposure to TSE - Contactable Group

There is a small sub group of possibly exposed people which the Panel considers to be at sufficient risk to warrant public health action. It is proposed that these people are contacted and informed about their exposure so that they can be advised not to donate blood or organs, and so that they can alert their healthcare provider to the potential exposure if they require any surgical procedure in the future, including any dental or ophthalmic procedures.

Mechanisms will be put in place to alert the National Blood Service and Organ Donation bodies when a contactable individual is identified to prevent these individuals from donating blood, organs and tissues. In addition, the individual's clinician or general practitioner will be informed of the potential exposure so that appropriate precautions can be taken in the event of the need for future medical interventions.

These individuals may, if they so choose, opt out of inclusion in the confidential database but may not prevent information being passed to the relevant healthcare providers to ensure protection of public health. This should be explained to them when they are informed of the possible exposure

The provision of an adequate mechanism for informing and counselling individuals within this contactable group is a crucial component of the Panel's proposals.

Providing publicity

The Panel proposes that effective publicity is provided to alert the public to the existence of the database and that information is provided on how someone could find out whether they are on the database, and how they can have their details removed if so desired.

Section 1: Introduction

Background

Transmissible Spongiform Encephalopathies (TSEs)

1.1 Human TSEs are rare and fatal neurological conditions that affect the nervous system. Creutzfeldt-Jakob Disease is one of this group of diseases, also known as the prion diseases. All types of human TSEs are associated with a conformational change in a protein called the 'prion protein'. The abnormal form of this protein accumulates in the brain in these disorders and is associated with the death of nerve cells.

1.2 The commonest form of human TSE is sporadic CJD, which affects approximately one per million of the population per annum across the world and accounts for around 85% of all cases of CJD. Around 60 cases of sporadic CJD are reported annually in the UK. The underlying cause of sporadic CJD is not known. Around 10% of human TSE cases occur as familial diseases (Familial CJD, Gerstmann-Sträussler-Scheinker syndrome and Fatal Familial Insomnia). These disorders are associated with mutations in the prion protein gene and are inherited as autosomal dominant conditions. Rarer forms of TSEs include acquired diseases such as Kuru (confined to the Fore tribe in Papua New Guinea), and iatrogenic CJD transmitted between people by medical and surgical procedures including injections with human pituitary hormones, dura mater (membrane covering the brain) grafts, and very rarely by neurosurgical instruments.

1.3 Variant CJD (vCJD) is a novel form of human TSE which was first recognised in 1996. This new disease is associated with the same transmissible agent that is responsible for Bovine Spongiform Encephalopathy (BSE). Experimental studies have shown that the BSE agent is not related to sporadic CJD. There have been over 140 confirmed or probable cases of variant CJD in the UK[i]. Variant CJD is thought to have resulted from the consumption of BSE-contaminated food products. Most of the population of the UK has probably been exposed to BSE, and it is not known how many people have been infected but currently show no signs of neurological disease. Estimates range from a few hundred to many thousands. Variant CJD also differs from other human TSEs in that the transmissible agent accumulates outside the central nervous system in the lymphoid tissues throughout the body (see section 2).

Transmission of CJD

1.4 While there is no evidence that any type of CJD can spread between people through normal social contact, sporadic CJD has been transmitted between patients undergoing certain medical treatments. Transmission has followed neurosurgical procedures, corneal transplant operations and

[i As of Octboer 2003, 143 definite and probable cases of variant CJD had been reported to the UK National CJD Surveillance Unit]

treatment with hormones prepared from human pituitary glands. One of the reasons that transmission may occur is that prion proteins are resistant to normal methods of decontaminating surgical instruments.

1.5 Variant CJD has not yet been shown to be transmitted through surgical operations, or blood or tissue donations. However, it is a new disease, and there is no practical screening test to detect it during its (probably) long incubation period. This means that it may be too early to detect any cases that may have been transmitted between individuals.

Action to prevent person to person transmission of CJD through healthcare

1.6 Guidance has been issued on what action should be taken to prevent TSE being transmitted from patients who have symptoms of TSE or who have a recognised specific risk of developing a TSE **(Annex 1)**. Actions include destroying surgical instruments used on these patients[3] and not donating their blood, tissues or organs to other patients[4].

1.7 However, it is more difficult to prevent transmission of sporadic or variant CJD from patients who are, unknowingly, incubating the disease. This is relevant when patients diagnosed or suspected of having CJD are found to have undergone surgical procedures or donated blood, tissues or organs in the past.

1.8 For procedures performed some years ago, most of the risk from instruments contaminated with prion protein is likely to have already occurred. However, as prion proteins resist standard decontamination procedures, it is possible that such instruments could continue to pose a risk to future patients.

1.9 This situation is difficult to manage as it may not be possible to identify which instruments were used in a particular operation carried out some time ago. To remove all possibly remaining risk one would need to destroy any instrument that might have been used on a patient with CJD. In practice this could leave surgical units unable to function.

1.10 Some people with CJD may have donated blood, tissues or organs before they developed symptoms. The long incubation period of CJD makes it likely that such donated tissues will have been used by the time the donors are diagnosed with CJD.

1.11 Action has been taken to reduce the risk of transmitting variant CJD through plasma derivatives such as clotting factors and immunoglobulins. Since 1998 the plasma used to make these products has been imported from countries with little or no BSE. Donors in these countries are highly unlikely to be incubating variant CJD.

1.12 Much remains to be discovered about the infectivity of different tissues and the effect of decontamination processes on prion proteins. As the risk of transmitting CJD in healthcare settings is unknown, a precautionary approach to the management of the possible risk is advisable. However, the unknown risk of acquiring CJD from medical procedures needs to be

considered alongside the background risk to the UK population following exposure to BSE. The known risks and benefits inherent to surgery and other medical procedures must also be considered.

1.13 There are ethical and practical issues around informing people that they might have been put at risk. Some of these people may have a relatively high chance of having been exposed to CJD infection. They will need to be informed so that they do not themselves transmit the infection to other patients. Other people will have a smaller risk of acquiring the disease. For this group, information about possible exposure risks should be made available to those who want it. However, this information potentially brings with it a great burden as CJD is a fatal disease for which there is as yet no cure.

1.14 There is currently no pre-symptomatic test available for sporadic or variant CJD. Familial forms of TSE can be detected before the onset of clinical disease if the relevant genetic mutation is identified in the prion gene. All forms of the disease can be diagnosed once clinical signs and symptoms have developed through neurological examination, MRI scans of the brains and other diagnostic tests. In vCJD, tonsil biopsy has been performed on a number of patients in order to detect the disease-associated form of the prion protein and, in exceptional cases, a brain biopsy may be performed in order to exclude the possibility of an underlying treatable condition in patients with suspected CJD.

Aims

1.15 This document provides a framework for managing incidents that arise when individuals have undergone medical procedures or have donated blood, tissues or organs and are subsequently diagnosed or suspected of having TSEs. This framework has five main aims:

- To protect patients from the risk of acquiring TSEs in healthcare settings.
- To ensure that those who might have been exposed are informed in a manner appropriate to their level of risk.
- To ensure that those who might have been exposed to lower levels of risk, while not being actively informed, are able to find out about their exposure if they so wish.
- To increase knowledge about the risk of transmitting TSEs in healthcare settings so as to be better able to manage any risk to individuals and to the public health.
- To ensure that the public is informed about possible risks of acquiring TSEs through healthcare.

Purpose of document

1.16 The CJD Incidents Panel is an expert group set up by the Department of Health on behalf of all UK health authorities to advise all those bodies responsible for the provision and delivery of health care on the most appropriate action to take to handle incidents involving potential

transmission of Creutzfeldt-Jakob Disease (CJD) between patients through clinical interventions, including via surgical instruments, tissues, organs and blood. The Panel advises on incidents throughout the UK.

1.17 This document sets out the basis for decision making by the CJD Incidents Panel, and should be used by public health teams, infection control teams, clinicians, trust managers and other professionals responding to local incidents.

1.18 This framework sets out what is known about the risk of transmitting TSEs through invasive medical procedures including blood donation. It then describes how incidents should be identified and investigated, and the basis for the Panel's advice on the public health actions to be taken. The final section suggests how public communication should be carried out.

1.19 Current scientific uncertainties mean that this framework will evolve, being revised as scientific research proceeds.

1.20 This guidance should be seen in the context of other policy and advice on preventing the spread of TSEs in healthcare (**Annex 1**).

Principles

1.21 Incidents should be managed according to the following principles:

- To protect patients from the risk of acquiring TSEs in healthcare settings.
- To provide consistently high quality advice and information to people who may have been put at risk
- To respect where possible the wishes of those who do not want to be informed.
- To be open about the risk of acquiring TSEs in healthcare settings and the scientific uncertainties surrounding this risk.
- To increase knowledge about the risk of spreading TSEs through medical procedures.
- To protect the confidentiality of infected patients and those at risk of acquiring TSEs.
- To ensure that, wherever possible, actions taken to protect the public health do not prejudice individual patient care.

Section 2: Supporting Evidence

Introduction

2.1 This section describes what is currently known about the risk of transmitting variant Creutzfeldt-Jakob Disease (vCJD) or sporadic CJD through medical interventions. While some of our understanding is based on direct evidence on variant CJD or sporadic CJD in humans, more is known about how other Transmissible Spongiform Encephalopathies (TSEs) behave in animal models.

2.2 Little work has been carried out on tissue infectivity in familial TSEs or iatrogenic CJD. This document assumes that infectivity in these diseases resembles that found in sporadic CJD.

2.3 Broadly, four inter-relating factors determine whether the use of a surgical instrument is likely to transmit CJD infection between patients. These are:

- The infectivity of the tissues in the patient with CJD that come into contact with instruments.
- The amount of infectivity remaining on the instruments following decontamination.
- Which tissues in subsequent patients come into contact with the instruments.
- The susceptibility of subsequently exposed patients.

2.4 In a similar way, the likelihood of transmitting CJD through blood or tissue donation depends on the infectivity of the donated blood and other tissues, the amount of infectivity remaining after processing, the amount of blood or tissue that is transferred to the recipient patients and the susceptibility of recipient patients.

2.5 A key element affecting the transmission of an infection is the relationship between the dose received and the 'response' to it – i.e. the chance of becoming infected. The risk assessments are based on a linear dose-response relationship; i.e. the chance of infection is proportional to the dosage received, with no lower threshold. This assumption has been endorsed by SEAC as a provisional working model and has been used for the basis of risk calculations.

Infectivity of tissues in CJD

2.6 There is a growing body of experimental evidence on which tissues accumulate abnormal forms of the prion protein and which may transmit CJD. There is also epidemiological evidence on the transmission of sporadic CJD through medical procedures involving different tissues.

2.7 Most of the experimental research has been carried out using animal models and TSEs other than CJD. Only a small number of studies have examined the behaviour of CJD in humans. Because of this, the available evidence has been categorised according to its likely relevance to

transmission of CJD in healthcare. Studies considered to be most relevant are those that have demonstrated infectivity in the tissues of patients with CJD. Studies considered to be least relevant include those that have detected infectivity in tissues of animals infected with TSEs such as scrapie (Table 1). This classification does not reflect the quality of the studies considered.

Table 1 Relevance of experimental evidence

Experimental evidence	Relevance of evidence
CJD in human tissue: infectivity demonstrated	**A**
CJD in humans: epidemiological evidence	**B**
CJD in human tissue, accumulation of abnormal prion protein detected	**C**
TSE in animal model, infectivity demonstrated	**D**

Variant CJD

The brain and spinal cord

2.8 Brain tissue of patients who have died of variant CJD has the highest level of infectivity of all the tissues studied[5]. **A**

2.9 The brain and spinal cord tissue have also been found to have the highest levels of infectivity in studies conducted on scrapie-infected mice,[6]. The dura mater of scrapie-infected hamsters[7] has also been shown to transmit infection. **D**

2.10 Experiments performed on scrapie-infected mice indicate that abnormal prion protein in the brain and spinal cord appears later in the incubation period than in lymphoid tissue[8]. **D**

The eye

2.11 Recent research has detected abnormal prion protein (characterised predominantly by its unusual resistance to protease digestion and therefore often referred to as PrP-res) in the optic nerve and retina of patients with variant CJD[9], [10]. PrP-res was not detected in the sclera, vitreous humour, lens, aqueous humour, iris or cornea. It is not known how levels of PrP-res relate to tissue infectivity. **C**

2.12 Studies on scrapie-infected hamsters indicate that infectivity levels in the optic nerve and retina are comparable with levels in the brain[11]. Lower levels of infectivity are present in the cornea, pigment epithelium/choroid and lens. This animal model experiment also suggested that infectivity is present in the brain and eye before the signs of disease. **D**

2.13 Experiments on hamsters infected with transmissible mink encephalopathy also indicate that the cornea is less infective than brain

tissues[12]. This study did not demonstrate infectivity in the aqueous humour. **D**

2.14 Infectivity has been detected in eye tissues in experimental scrapie at a similar point in the incubation period as it is found in the brain[13]. **D**

Olfactory system

2.15 PrP-res has been detected in olfactory epithelium in sporadic CJD patients at post mortem[14]. No reports are available for variant CJD but it is reasonable to assume that the finding in sporadic CJd would be applicable to variant CJD. **C**

Lymphoid tissue

2.16 Recent research has found that the spleen and tonsil have similar levels of infectivity in variant CJD and that these levels are 100 to 1,000 times lower than infectivity levels in the brain [5]. **A**

2.17 Other research has indicated that levels of PrP-res are higher in the tonsils than in other lymphoid tissues[9]. **C**

2.18 The lymphoid tissue is involved during the incubation period of variant CJD infection. Abnormal PrP has been detected in the appendix of two patients on whom an appendicectomy was carried out before symptoms of variant CJD developed[15, 16]. **C**

2.19 The lymphoid tissue continues to be involved during clinical disease, and abnormal PrP has been detected in the tonsil, spleen and lymph nodes of people who have died of variant CJD and in tonsil biopsies of patients with symptomatic disease[17]. **C**

2.20 Infectivity has been detected in the lymphoid tissue of scrapie-infected mice and sheep early in the incubation period [8 18]. Infectivity levels in the lymphoid tissue of scrapie-infected mice have been found to be lower than in brain and spinal cord tissue. [6] **D**

Other tissues

2.21 Studies on peripheral nerve tissue from four patients with variant CJD did not detect abnormal $PrP^{9,19}$ Abnormal prion protein has been detected in dorsal root ganglia and trigeminal ganglia in variant CJD[20]. **C**

2.22 Research on other peripheral tissues has detected low levels of PrP-res in the rectum, adrenal gland and thymus of a single patient with variant CJD. Levels of P^rP^{res} in these tissues were much lower than that found in brain tissue [9]. **C**

2.23 The dental tissues of three patients who died of variant CJD have been investigated. Abnormal prion protein was not detected in the gingival (0/3), dental pulp (0/2) or alveolar nerve (0/2) of these patients [21]. P^rP^{res} was identified in the trigeminal ganglia, but not in the peripheral branches of the nerve in the gum and dental pulp. **C**

2.24 Infectivity has been demonstrated in the dental tissue of scrapie-infected hamsters that were in the clinical stage of the disease[22]. This experiment indicated that infectivity levels in the gingival and pulp tissues were lower than in the trigeminal ganglia. **D**

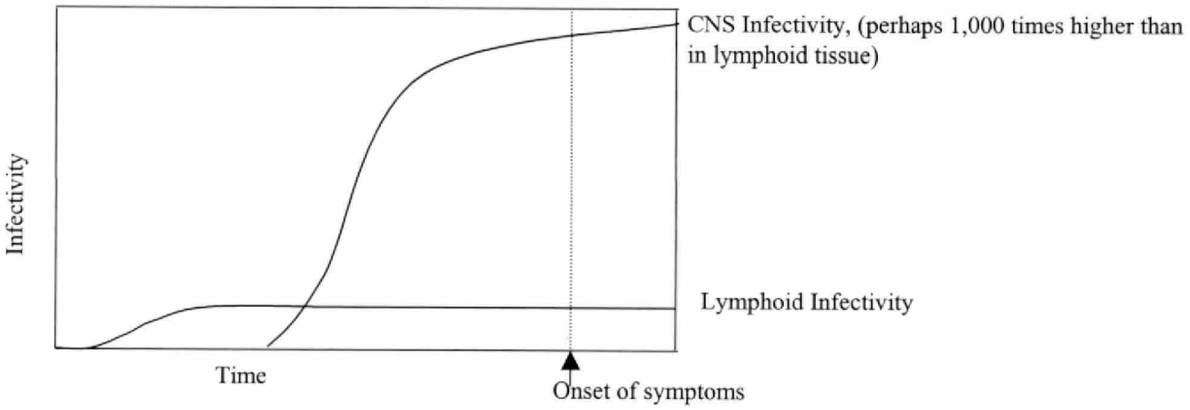
2.25 Other studies on scrapie-infected mice indicate that gingival tissues are infective, although experimental transmission was only achieved with difficulty. [23] [24] **D**

Disease progression

2.26 The incubation period for variant CJD is not known, but the median incubation period could be between 10 and 30 years. For practical purposes, this is taken to be any time since onset of the BSE epidemic in cattle. Although it is acknowledged that some BSE cases may have preceded this date, 1980 is taken as the earliest date at which individuals were likely to have been exposed to BSE agent. Extrapolating from animal models, the distribution of abnormal PrP and infectivity in variant CJD is expected to change as the infection progresses.

2.27 The expected time course for the changes in infectivity in different tissues in variant CJD is shown schematically in Figure 1.

Figure 1 Probable pattern of tissue infectivity in variant CJD, based on scrapie models



Route of transmission

2.28 Disease transmission depends not only on how much infectivity is present in the tissue, but also on where in the recipient the tissue is deposited. Animal experiments indicate that the most efficient transmission route is directly into the brain (intracerebral inoculation) [25] [26] [27]. **D**

2.29 This document follows the assumptions made in the surgical risk assessment[1], that transmission of variant CJD via material deposited into brain, spinal cord or posterior eye is at least ten times more efficient than if similar material is deposited into any other site. The same assumption is made for sporadic CJD.

Conclusions on tissue infectivity in variant CJD

2.30 The infectivity levels in different tissues in variant CJD are uncertain. However, assumptions may be based on the limited amount of evidence that is available. This document builds on the infectivity assumptions used in the surgical risk assessment[1] endorsed by SEAC. These conclusions are described in Table 2.

Table 2 Infectivity estimates in variant CJD

Central Nervous System (CNS)
Infectivity within the CNS is low in the early incubation stage, but increases as disease develops[a]. Infectivity levels of 10^8 i/c ID_{50}/g[b] may occur in the last 40% of the incubation period and increase to 10^9 i/c ID_{50}/g, or even 10^{10} i/c ID_{50}/g during clinical disease.
Eye
The retina and optic nerve are thought to have infectivity levels that could be as great as that found in brain tissue. Other parts of the eye (cornea, lens, and conjunctiva) are thought to contain 10 to 10^2 times less infectivity than brain tissue.
Infectivity in the eye is believed to increase as disease develops, with the levels cited appearing in the last 40% of the incubation period. A further 10-fold increase may also occur in the final year before the onset of symptoms.
Olfactory epithelium
The information on this tissue is very limited. The presence of abnormal PrP in the olfactory epithelium of 9 sporadic CJD cases has been described by one research group. Until more information is available, it is reasonable to assume that there is a medium level of infectivity in this tissue in CJD of all types, with the same time-course as for the brain and eye.
Lymphoid tissue
From early in the incubation period until death, infectivity levels of $10^6 - 10^7$ i/c ID_{50}/g may be widely dispersed in the lymphoid tissue.
Other Tissues
Other tissues may have some infectivity but at much lower levels than CNS, eye or lymphoid tissues.

a Infectivity is expressed as an ID_{50}. This is the dose that is expected to cause disease in 50% of the recipients to whom it is administered. A pre-script indicates the route of administration. Thus for a tissue that contains 1 i/c ID_{50}/g, one gram of tissue contains a dose which, when given by intracerebral inoculation, is expected to infect 50% of recipients.

b 10^8 is a mathematical expression for 10 x 10 x 10 x 10 x10 x 10 x 10 x 10, or 100,000,000

2.31 These infectivity estimates have been combined with possible transmission routes to give infectivity estimates for exposed tissues in subsequent patients. These estimates in Table 3 assume that instruments come into contact with similar tissues in the CJD patient and subsequent patients.

Table 3 Potential infectivity in variant CJD, by source tissue and site of exposure

Source tissues and tissues exposed during surgery	Disease stage	Infectivity [ID_{50} / g]
CNS to CNS (or retina or optic nerve)	First 60% of incubation period	$0 - 10^4$
	Last 40% of incubation period and during clinical disease	10^8 (this could increase to 10^9 in the final year and to 10^{10} after the onset of symptoms)
Other parts of eye to other parts of eye olfactory epthelium	First 60% of incubation period	$0 - 10^4$
	Last 40% of incubation period and during clinical disease	$10^5 - 10^6$
Lymphoid tissue to lymphoid tissue	All of the incubation period and during clinical disease	$10^5 - 10^6$
Remaining tissues, including blood	All of the incubation period and during clinical disease	$0 - 10^4$

Sporadic CJD

The brain, spinal cord, eye and olfactory epithelium

2.32 Abnormal PrP has been detected in the brain, spinal cord[28], eye[10] and olfactory epithelium[14] of patients with sporadic CJD. High levels of infectivity have also been found in the brain and eye tissue of patients who have died of sporadic CJD[29]. **A, C**

2.33 There have been 267 reports of transmission of sporadic CJD by medical procedures throughout the world[30]. These have followed treatment with growth hormone, dura mater grafts, neurosurgery, treatment with gonadotrophin, corneal transplants and stereotactic EEG needles. These data are summarised in Table 4. **B**

Table 4 Global cases of iatrogenic transmission of CJD (up to July 2000) [30]

Mode of infection	Number of patients infected
Tissues/Organs	
Corneal transplant	3[#]
Growth Hormone	139
Dura mater graft	114[*]
Gonadotrophin	4
Surgery/invasive procedures	
Neurosurgery	4[ii±]
Stereotactic EEG	2

[#]One definite, one probable and one possible case.

[*]In two cases, dura was used to embolise vessels of non-CNS tissues, rather than as intracranial grafts.

[±]Contaminated neurosurgical instruments

2.34 The level of abnormal PrP in the brain, spinal cord, retina and optic nerve in sporadic CJD is thought to be similar to levels in variant CJD.

2.35 Experiments in which corneas from humans and guinea pigs infected with CJD have been transplanted into animals indicate that corneas can transmit CJD[31 32]. **A, D**

2.36 Transmission of sporadic CJD has been reported after corneal graft operations [33 34]. It is not known whether other parts of the anterior eye are infective. **B**

2.37 The information on the olfactory epithelium is very limited. The presence of abnormal PrP in the olfactory epithelium of 9 sporadic CJD cases has been described by one research group. Until more information is available, it is reasonable to assume that there is a medium level of infectivity in this tissue, with the same time-course as for the brain and eye. **C**

Other tissues

2.38 Most evidence indicates that in sporadic CJD tissues outside the nervous system, including the lymphoid tissue, do not contain significant levels of infectivity [17] **C**.

2.39 However, one report suggested that low levels of infectivity are present in the spleen, lymph nodes, kidney, liver and lung tissues of some patients with sporadic CJD[29]. This report did not demonstrate infectivity in several other peripheral tissues including peripheral nerve, intestine and blood. **A**

[ii] Personnal communication Professor R Will

2.40 Interpretation of the positive findings is uncertain and further work is needed to confirm or refute these observations. This document assumes that if any tissues outside the nervous system are infective in sporadic CJD, then it is only with low levels of infectivity.

2.41 A recent experiment on dental tissues from patients with sporadic CJD did not detect abnormal PrP^{35} but further work is needed in this area. **C**

2.42 The incubation period for sporadic CJD is not known. For practical purposes, this framework document assumes that the clinical symptoms are not apparent until 20 years after the disease process is initiated. From animal models it is judged that the last 40% of this period represent the period of time, prior to diagnosing the disease, that the individual presented a significant risk to others. This assumption is used to estimate the duration of infectivity of tissues such as the brain and eye.

Conclusions on tissue infectivity

2.43 The likely infectivity of tissues from patients with sporadic and variant CJD is summarised in Table 5. These relative infectivity levels are based on current knowledge and advice from SEAC.

Table 5 Tissue infectivity in sporadic and variant CJD

Tissue	Sporadic CJD	Variant CJD
Brain, spinal cord, cranial and spinal ganglia, dura mater	High	High
Optic nerve and retina	High	High
Other eye tissues, olfactory epithelium	Medium	Medium
Appendix	Low	Medium
Tonsil	Low	Medium
Spleen	Low	Medium
Other lymphoid tissues	Low	Medium
Blood [1]	Low	Low
Other tissues, including dental pulp and gingival tissue	Low	Low

High: $>=10^7$ ID_{50}/g; Medium 10^4-10^7 ID_{50}/g; Low $<10^4 ID_{50}$/g

[1] See section on infectivity in blood.

Infectivity transmitted via instruments

2.44 Instruments may be contaminated with prion protein during contact with infective tissue in surgery. There is concern that prion protein can resist normal decontamination processes and that infectivity may remain on instruments when they are used on other patients.

2.45 Little evidence is available in this area which is the subject of a research programme. Until further evidence becomes available this document builds on the assumptions made in the surgical risk assessment[1] endorsed by SEAC.

2.46 The amount of infective material contaminating an instrument following surgery depends on the type of instrument and the tissues with which it is contaminated. This document follows the assumptions used in the surgical risk assessment[1] that an average of 10 mg of material could remain on an instrument. This is derived from an estimate that 5 mg may adhere to an instrument with plane surfaces, such as a blade[36]. This is an area of considerable uncertainty, but the amount of material contaminating an instrument directly after surgery is less important than the amount that remains after decontamination.

2.47 A *decontamination cycle* for a surgical instrument involves two stages; physical cleaning, typically using a mechanical washer / drier; followed by inactivation of any remaining infectious material, e.g. by autoclaving.

Cleaning

2.48 Instruments undergo a large number of decontamination cycles during their working lives. Studies on instruments with flat surfaces indicate that the first cycle of cleaning may reduce the amount of protein on an instrument by a thousandfold [37]. However, instruments with serrated edges and hinges, and others with narrow lumens such as flexible endoscopes, are much more difficult to clean. This guidance follows the assumptions made in the Risk Assessment[1] that cleaning is likely to reduce the infectivity remaining on an instrument by a factor of 100 to 1,000.

2.49 Subsequent cleaning rounds are likely to be much less effective as any material that has survived the first cleaning cycle may have been baked on during further processing or in the case of flexible endoscopes, fixed to the equipment on by the chemical agents used in processing. There is little experimental evidence on how much would remain. This document follows the assumptions made in the surgical risk assessment[1] that subsequent cleaning cycles could reduce the amount of infectivity remaining on an instrument by as much as a factor of 100.

2.50 This document uses the assumption of the ACDP/SEAC Joint Working Group on TSEs, that cross-contamination of instruments during cleaning was unlikely to occur. This was because in a wet environment, and in the presence of detergents, proteins are unlikely to migrate from one surface and stick on another.

Inactivation

2.51 Inactivation is generally carried out by high pressure steam autoclaving of instruments. Different autoclaving processes vary in their effectiveness in inactivating prion protein [38]. The effectiveness may be altered by small differences in temperature[39]. This document uses the assumptions made

in the Risk Assessment[1], that the first autoclaving cycle would achieve a 10^3 to 10^6-fold reduction in infectivity. **C**

2.52 Subsequent autoclaving cycles may have less additional effect. This document follows the assumptions made in the surgical risk assessment[1] that these could achieve up to 10^3-fold reduction in infectivity.

2.53 It is possible that even following a great many cycles of use and decontamination, some infectivity remains on instruments. This document assumes that any infectivity that has resisted removal and remained on instruments, would be firmly attached and unlikely to transfer to subsequent patients during normal surgical procedures. This document follows the provisional assumptions made in the surgical risk assessment[1], that infective material must be transferred from an instrument into a subsequent patient for disease transmission to take place. There is some limited evidence that, under certain circumstances, infection could arise from contact with the instruments without the transfer of infective material[40]. Until more evidence supporting this alternative mechanism is available the Panel is using the transfer model accepted by SEAC.

Combined effect of cleaning and inactivation

2.54 This document follows the assumptions made in the surgical risk assessment[1] that the first washing and autoclaving cycles combined would achieve at least a 10^5-fold reduction in infectivity. Subsequent cycles may have much less effect. In ideal conditions decontamination processes are likely to be even more effective but these cautious estimates allow for less than optimal working practices.

2.55 A major research programme into instrument decontamination is underway and the results of these studies may provide some of the basic information that is currently lacking in this area. This document will be revised as new evidence becomes available.

2.56 The framework document assumes that infectious and non-infectious material is removed from instruments in similar proportions. There are as yet no data to suggest otherwise.

2.57 The likely effectiveness of instrument decontamination is summarised in Table 6. This summarises the assumptions made in the surgical risk assessment[1] endorsed by SEAC.

Table 6 Effectiveness of instrument decontamination

Variable	**Value /range**
Initial amount of material on instruments (mean, per instrument)	10 milligrams
Cleaning (washing / disinfecting)	
Reduction in amount of material after first cleaning	$10^2 - 10^3$ fold reduction

Reduction in amount of material after subsequent cleanings	$0 - 10^2$ fold reduction
Deactivation (sterilising / autoclaving)	
Reduction in infectivity after first autoclaving	$10^3 - 10^6$ fold reduction
Reduction in infectivity after subsequent autoclaving	$0 - 10^3$ fold reduction

Type of instruments used

2.58 Decontamination is affected by an instrument's material and construction – whether it has joints, lumens, serrated jaws, ratchets etc. (**Annex 2** categorises types of instrument by their ease of decontamination).

2.59 In some cases, only parts of instruments may come into contact with infective tissues (for example drill bits or the probe in a stereotactic frame). These may cross-contaminate the rest of the instrument.

2.60 Some instruments cannot be autoclaved. These include flexible endoscopes and other optical equipment. Glutaraldehyde is sometimes used to decontaminate rigid endoscopes. However, this is likely to stabilise any prion protein present on the instruments.

2.61 Fibreoptic endoscopes are more difficult to decontaminate effectively than other instruments, such as normal stainless steel instruments, and this problem is increased if biopsies are carried out using endoscopes. Endoscopes that come into contact with lymphoid tissue and other infective tissue may continue to pose a risk to subsequent patients despite going through many cycles of use and decontamination.

2.62 The Joint TSE Working Group of the Advisory Committee on Dangerous Pathogens and SEAC is currently undertaking an assessment of the risks of transmission of CJD by various types of endoscopes. The Panel's framework document will be updated when this assessment is available.

Modelling scenarios

2.63 Scenarios modelling the infection risk for subsequent patients following surgery on an 'index' patient with CJD are illustrated in Figures 2-5. These scenarios use different tissue infectivity levels in the 'index' patient and different proportions of contaminating prion protein transferred from the instruments to subsequent patients. In each scenario the risk of transmitting infection drops dramatically for subsequent patients and is close to zero before the 10^{th} reuse of an instrument.

2.64 These scenarios have been prepared by the Economics and Operational Research Division of the Department of Health, and are based on the following assumptions:

- 20 instruments are used per operation.
- Each instrument used is initially contaminated with 10 mg of tissue.
- The first decontamination cycle reduces contamination by a factor of 10^5
- Each subsequent decontamination cycle reduces contamination by a factor of 10.
- The instruments contact the same type of tissue in the CJD and subsequent patients.

It should be stressed that the figures 2 – 4 are modelling scenarios based on assumptions drawn from the limited amount of available evidence. The Panel has used those scenarios that they deem reasonable but the figures generated remain uncertain.

The graphs show how the chance of each subsequent patient being infected reduces as instruments are used, decontaminated and re-used again.

Figure 2 Scenario modelling of the decreasing risk of infection with successive re-uses.

Tissue Infectivity 10^{10} ID_{50}/g (e.g. CNS in patients with symptoms of CJD).

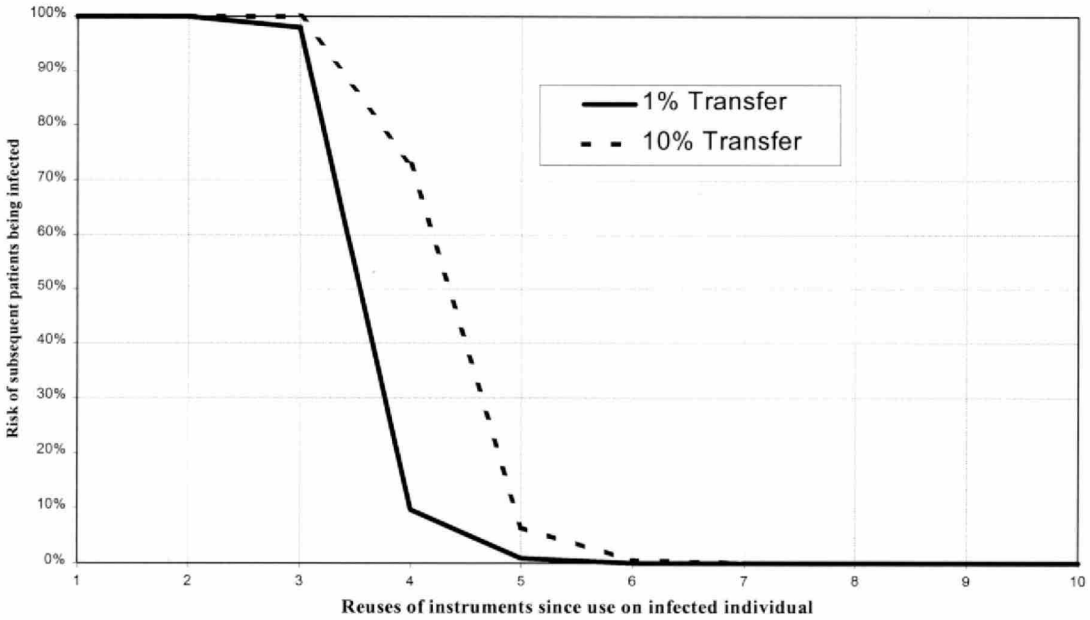


Figure 3 Scenario modelling of the decreasing risk of infection with successive re-uses.

Tissue Infectivity 10^8 ID_{50}/g (e.g. CNS in patient in the later stages of incubation period)

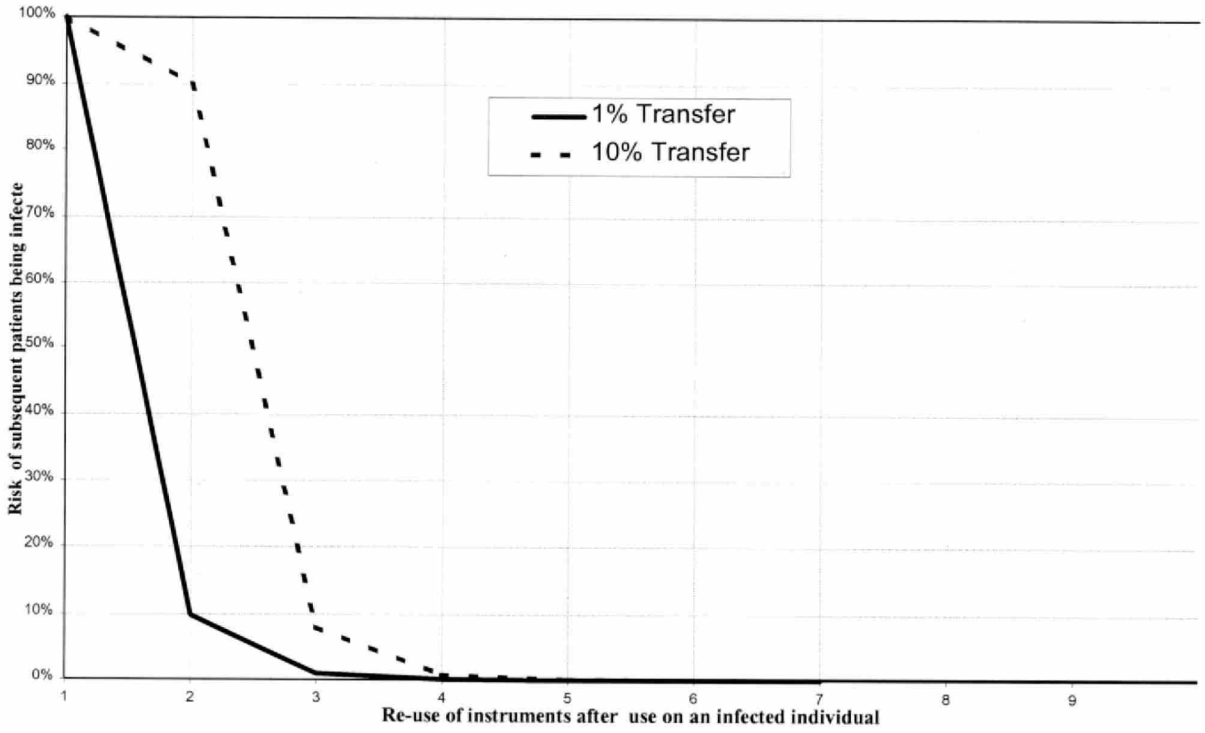


Figure 4 Scenario modelling of the decreasing risk of infection with successive re-uses.

Tissue Infectivity 10^6 ID_{50}/g (lymphoid tissue in patient at any stage of vCJD infection; anterior eye or olfactory epithelium during the last 40% of the incubation period of any form of CJD; more pessimistic assumption)

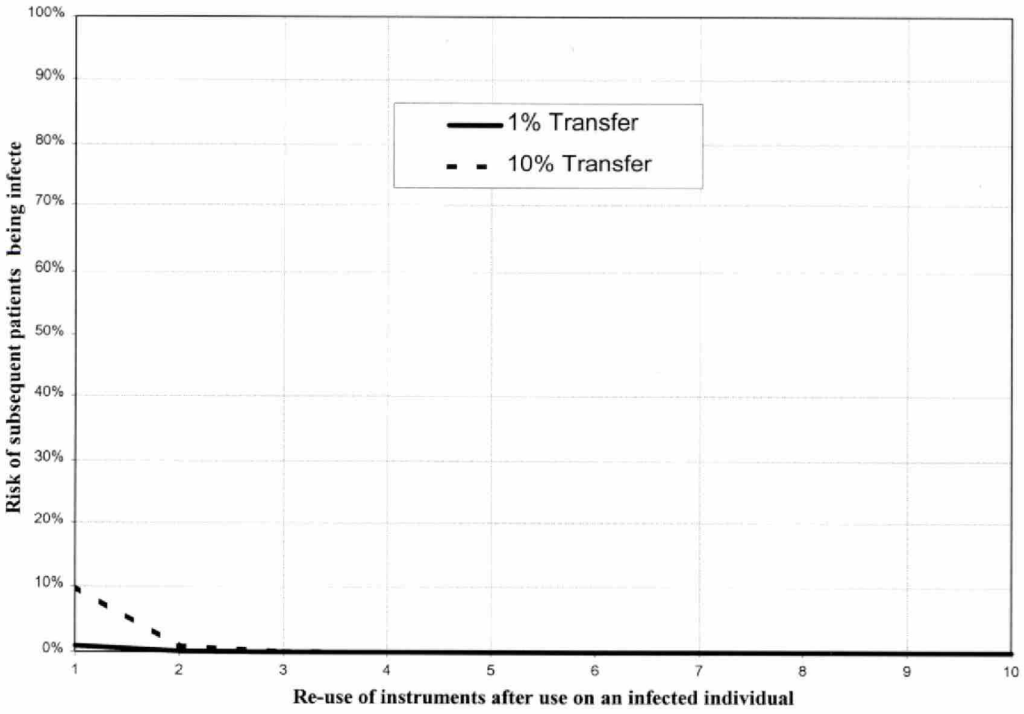
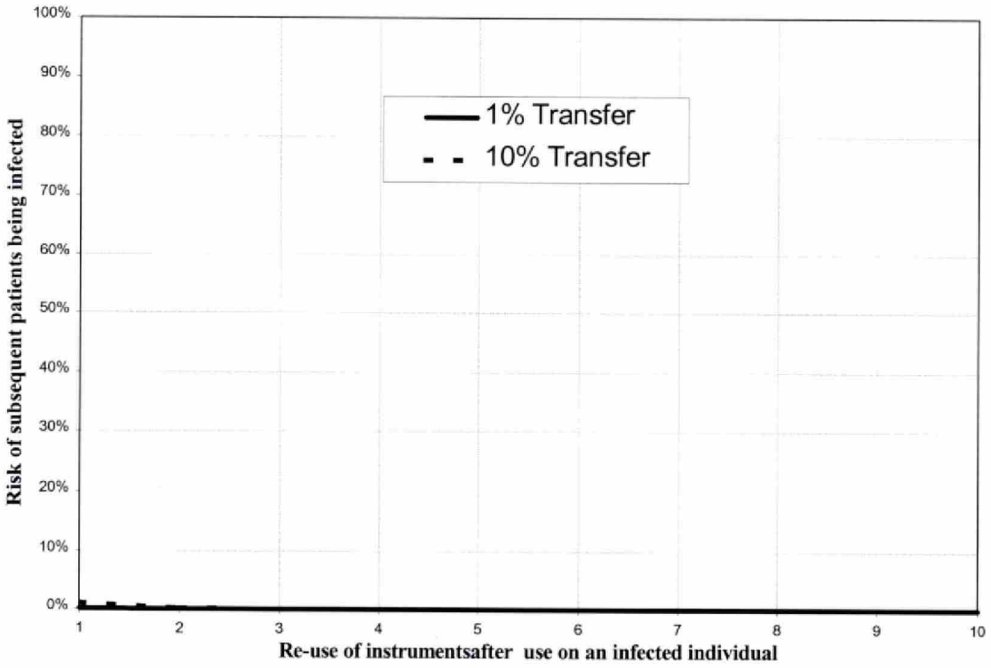


Figure 5 Scenario modelling of the decreasing risk of infection with successive re-uses.

Tissue Infectivity 10^5 ID_{50}/g (lymphoid tissue of patient in any stage of vCJD infection; olfactory epithelium or anterior eye during the last 40% of the incubation period of any form of CJD; less pessimistic assumption)



Conclusions

2.65 On the basis of the preceding evidence and reasoning, most instruments that have gone through ten cycles of use and decontamination are unlikely to pose a significant risk. However, this is an area of active research, and the CJD Incidents Panel should consider the type of instrument used in each incident, as some are particularly difficult to decontaminate.

2.66 The Panel is of the view that healthcare providers should ensure that decontamination procedures are within Department of Health recommendations for best practice, or Glennie standards in Scotland [41]. [42,43]

Dental procedures

Variant CJD

2.67 This section is based on a Risk Assessment for vCJD and dentistry which was carried out by the Economics and Operational Research Division of the Department of Health[44].

2.68 It is possible that patients with variant CJD could transmit the infection through instruments used in dental procedures. This could happen in two ways: if instruments accidentally abrade the lingual tonsils, or via instruments that come into contact with dental pulp.

Transmission through tonsillar abrasion

2.69 Infectivity has been demonstrated in the tonsils of patients with variant CJD (paragraphs 2.16 to 2.20). The risk assessment considered whether accidental abrasion of an infective patient's lingual tonsil could be a transmission route for variant CJD.

2.70 The risk assessment concluded that the risk of transmitting variant CJD via tonsillar abrasion is remote. For comparison, a single dental procedure on an infective patient would be about 10,000 times less likely to transmit variant CJD than a tonsillectomy, even with very pessimistic assumptions about the risks of abrasion.

2.71 The risk assessment found that even if a patient incubating variant CJD were to undergo a dental procedure, the instruments would be very unlikely to infect anyone else in this way – the chance being about 1 in 20,000 for indefinite instrument re-use.

Transmission through dental pulp

2.72 While abnormal prion proteins have been found in dental tissue in animal TSE models, this has not been demonstrated in the dental pulp of humans with variant CJD (paragraphs 2.23 to 2.25).

2.73 Even so, the risk assessment considered the possible risk of transmitting variant CJD if infectivity were to be present in human dental

pulp. As an example, the analysis considered the re-use of dental files and reamers, items which are known to be difficult to clean effectively.

2.74 The risk assessment found that even under pessimistic assumptions, the risk of variant CJD being transmitted to another patient on contaminated files and /or reamers would be less than 1%. This compares with estimated risks of infection from 'first re-use' of instruments as high as 100% for CNS and posterior eye surgery, and 10% for lymphoid operations, when calculations are done on a similar basis.

2.75 Nevertheless, the assessment stressed the need for the best possible standards of decontamination, given the large numbers of dental procedures carried out each year.

Sporadic CJD

2.76 There is no evidence that abnormal prion protein is present in dental or tonsil tissue in sporadic CJD (see paragraphs 2.38 to 2.41). Dental procedures are not considered to pose a significant risk in patients with sporadic CJD.

Conclusions

2.77 Dental procedures are considered to be low risk for both sporadic and variant CJD. However, this assessment will be reviewed in the light of any new scientific evidence on infectivity in human dental tissues.

Estimates of infectivity of blood components and plasma derivatives

The risk assessment below is based on the 2003 blood risk assessment[2].

Definitions

2.78 This section deals with the potential infectivity of blood components and plasma derivatives produced from blood donated from people who go on to develop CJD.

2.79 Blood components are derived from a single blood or plasma donation or in the case of platelets, a small pool usually of about four donations. These are labile products with a short shelf life. Blood components include whole blood, red cell concentrates; platelets (cell fragments involved in blood clotting), granulocytes (a form of white blood cell), fresh frozen plasma, and cryoprecipitate (made by freezing and thawing plasma).

2.80 Plasma derivatives are prepared from human plasma pooled from a large number of donations. These products have a long shelf life and, unlike blood components, are licensed medicinal products. Plasma derivatives include clotting factors, immunoglobulins, albumin, and anti-thrombin.

Background

2.81 This document builds on the information summarised in the 2003 blood risk assessment[2], which has been accepted by SEAC and the Committee on the Safety of Medicines. This risk assessment will be reviewed to reflect new research on plasma derivatives and the effects of purification processes. This section will be revised as new information becomes available.

2.82 There is no epidemiological evidence that any form of CJD (familial, sporadic or variant CJD) has ever been transmitted as a result of treatment with blood components or plasma derivatives. Studies of recipients of blood donated by people who go on to develop sporadic CJD, and studies of sporadic CJD prevalence among haemophiliacs, have not demonstrated an increased risk of developing CJD[2, 45]. **B**

Variant CJD

2.83 In variant CJD the disease process involves many tissues, including the lymphoid tissue. There is however, no evidence that variant CJD can be transmitted by blood components or plasma derivatives. However, variant CJD is a new disease with a long incubation period, and it may be too soon for cases transmitted by this route to be detected.

2.84 The 2003 risk assessment[2] concluded that with the current level of knowledge it is not possible to draw any conclusions as to whether or not infectivity can be transmitted through products derived from human blood.

2.85 Evidence on the possible infectivity of blood in variant CJD is limited. One study has investigated whether blood from people with variant CJD can transmit the disease to mice[5]. This study did not detect infectivity in plasma or in buffy coat (a blood fraction rich in white cells and platelets). However, the methods used had a detection limit of about 200 human i/v ID_{50}s per ml, and therefore would not have detected levels of infectivity that could result in transmission of variant CJD in humans. **A**

2.86 Even the most sensitive method for detecting abnormal prion protein did not give positive results for a buffy coat preparation from the blood of a vCJD patient. However, this method is considered to be less sensitive than the mouse infectivity model. The detection limits of the techniques used meant that if any PrP-res was present, it must have been at a concentration 300,000-fold lower than that found in the patient's brain. **C**

2.87 Even low infectivity levels could be important because large quantities of blood and plasma derivatives are used to treat individual patients. These quantities greatly exceed the trace amount of protein remaining on surgical instruments after decontamination.

2.88 Interim results from a study on the transmissibility of BSE and natural scrapie between sheep by transfusion of whole blood and of buffy coat have indicated a transmission rate of about 20% [46]. Several of the successful transmissions were from donors who had not yet developed

symptoms of disease. This study is ongoing, and it is not yet possible to estimate the infectivity levels. **D**

2.89 The risk assessment was based on the levels of infectivity in blood components and plasma fractions estimated from results in animal models. The applicability of these data to vCJD infectivity in human blood is not known but the expert Committees agreed with DNV that these are the best data currently available. The estimates derived from the DNV assessment have therefore been used as the basis for the calculations in this framework document.

Whole blood

2.90 The infectivity of whole blood from vCJD cases is estimated to be 2 i/v ID_{50} per ml, based on tests on mice with CJD. The range, based on other animal experiments, could be 0.2 to 60 i/v ID_{50}/ml. Allowing for the possibility that blood is not infective, the range would be 0 – 60 i/v ID_{50}/ml.

2.91 Infectivity in blood is assumed to be constant throughout the incubation period for variant CJD. For practical purposes, the earliest time that patients could start to incubate the disease is taken to be the onset of the BSE epidemic in 1980.

2.92 The route of administration affects the transmission of TSEs in animal models. The intravenous and intramuscular routes used for blood components and plasma derivatives are less efficient than direct inoculation into the brain. This document follows the assumption made in the blood risk assessment[2] report, that the intravenous route is 5 times less efficient than the intra-cerebral route. Recent studies by Brown et al suggest a comparable value[47].

Leucodepletion

2.93 The involvement of lymphoid tissues in variant CJD raises the possibility that white blood cells could contain infectivity. While this has not been demonstrated, leucodepletion (removal of white blood cells) has been carried out on all UK-sourced blood since 1999 as a precautionary measure. In the absence of convincing evidence, this guidance has adopted the judgement of DNV, that leucodepletion seen after donation may reduce infectivity of red cells by 2 orders of magnitude but does not affect the infectivity of other components.

Blood components

2.94 Most modern treatments use blood components rather than whole blood. The literature on infectivity of different components of blood was reviewed as part of the blood risk assessment. This concluded that studies carried out on familial CJD in mice provided the best available model for the distribution of infectivity in variant CJD in human blood[2]. However, this model may not be directly relevant to infectivity in the blood of humans with variant CJD. One recent study has reported experimental

transmission of experimental BSE and natural scrapie in a sheep model following transfusion. **D**

2.95 Other studies have examined infectivity in blood that has been 'spiked' with brain material from hamsters infected with scrapie. This model has also been used to investigate the effects of different processing steps on infectivity. However, these experiments may not give a true impression of the distribution of infectivity in blood in people with variant CJD. This guidance and the blood risk assessment have only drawn on data from these experiments when no other information is available.

2.96 Estimates for infectivity used in the blood risk assessment are reproduced in Table 7.

2.97 These results should be interpreted with some caution as the distribution of infectivity within blood in people with variant CJD may well differ from that found in mice infected with a familial human prion disease. Also, the fractionating procedures used in the mice experiments may not be directly comparable with those used for human blood.

Table 7 Possible infectivity levels of blood components in variant CJD

Component	**Infectivity per ml (iv ID_{50} /ml)**	**Infectivity per unit (iv ID_{50} /unit)**
Whole blood	2	900
Plasma	2	500
White cells + platelets	15	200
Red cells	0.01 - 1*	2-200*

*This depends on the processing used

2.98 Preparations of red cells, platelets and plasma contain varying amounts of the other components. Given the uncertainties over the infectivity values in general, and over how infectivity is distributed between white cells and platelets, this guidance assumes that the infectivity of platelet preparations is the same as the mixed white cell plus platelets fraction.

2.99 The figures in Table 7 are based on very uncertain estimates from the blood risk assessment [2] that are derived from the data from Brown *et al* 1998 [47].

2.100 Patients usually receive more than one unit in a transfusion, and may be transfused several times. Even so a patient is unlikely to receive more than one unit of a blood component from a particular donor with variant CJD.

Estimates of infectivity in plasma derivatives

2.101 Plasma is estimated to have approximately the same infectivity as whole blood, i.e. 2 ID_{50}/ml (see Table 7). The infectivity in plasma

derivatives depends on the size of the pool of donations used to manufacture the derivative, the effect of processing and the amount administered.

Size of donor pool

2.102 Tens of thousands of donations of plasma may be combined to prepare plasma derivatives, so greatly diluting any single infected donation. For example, if plasma derivatives are derived from a pool of 20,000 donations, then the infectivity in the starting product is estimated to be 0.5×10^{-4} iv ID_{50}/ml.

2.103 Specific immunoglobulins (e.g. anti-D, hepatitis B, tetanus, rabies, Varicella zoster) are produced from much smaller pools of donations. The number of donations used depends on the type of immunoglobulin and the producer, and ranges from less than 50 to 4,000. These pools may also contain more than one donation from the same donor.

2.104 In specific incidents, the size of the pool used should be used to calculate the potential infectivity of plasma derivatives.

Effect of processing

2.105 Plasma derivatives undergo various processing stages including cryoprecipitation, extraction with ethanol, precipitation, filtration, partitioning, virus inactivation and heat treatment.

2.106 A number of studies to assess the removal of TSE agent in the plasma fractionation process have been carried out by "spiking" the starting material with extracts from the brains of animals with a TSE. These suggest that a significant reduction in infectivity is achieved. However, concern has been expressed that the characteristics of any infectivity that might be present in blood could be quite different from that found in the spiked material. The Panel recommends taking a precautionary approach, using the risk assessment that is based on levels of endogenous infectivity and not correcting for any potential reduction by further processing.

Dose

2.107 A 'dose' of a plasma derivative may contain high concentrations of proteins. Some clinical conditions require repeated doses, so that large amounts may be given over a period of time. This is important as patients could receive multiple doses from the same possibly contaminated batch of plasma derivative. This document adopts the DNV assumption that the risks from such repeated doses of variant CJD would be additive over a one year period.

Infectivity

2.108 The risk from plasma derivatives is even more uncertain than from **blood components.

2.109 The blood risk assessment based its infectivity calculations on a combination of the low dose and spiking experiments of Brown et al 1998. It assumed that the infectivity in the end-product plasma derivatives is the

same as in the plasma fraction from which it was derived. The infectivity values in Table 8 are derived from the blood risk assessment, based on no clearance of infectivity beyond the initial fractionation.

Table 8 Estimates of the infectivity of plasma derivatives prepared from a pool including a donation from a patient who developed variant CJD

Derivative	Potential Infectivity[a]
Factor 8 (low specific activity)	0.1 ID_{50} per standard dose of 2000 iu
Factor 8 (highly purified)	0.2 ID_{50} per standard dose of 2000 iu
Factor 9	0.1 ID_{50} per standard dose of 1250 iu
Normal Immunoglobulin	0.08 ID_{50} per 90g intravenous dose
Albumin 20%	0.0006 ID_{50} per standard dose of 100ml
Anti-thrombin	1 ID_{50} per standard dose of 3000 iu

[a]These values are based on the total yields of products obtained from a typical plasma pool. Potential infectivity has to be calculated from individual production details and will be lower than those shown here. Specific calculations will need to be carried out for each batch of each product.

2.110 The blood risk assessment did not provide estimates of infectivity values for any other plasma derivatives.

Conclusions

2.111 While the pool size and processing details will need to be assessed for each incident, it seems clear that albumin is likely to have low infectivity levels.

2.112 Factor VIII, Factor IX, anti-thrombin and immunoglobulin may, however, be of concern. The management of incidents involving these, and other plasma derivatives is discussed in section 6.

2.113 These risks may need to be reassessed if research indicates that the less precautionary risk assessment for plasma derivatives, also proposed by DNV, is justified.

Sporadic CJD

2.114 There is no epidemiological evidence that sporadic CJD has ever been transmitted as a result of treatment with blood components or plasma derivatives[2]. **B**

2.115 There is a general consensus that blood components and fractionated plasma derivatives prepared from donors who go on to develop sporadic CJD, are unlikely to increase the risk of recipients developing the disease. This framework document has not attempted to further characterise this risk.

Susceptibility of subsequent patients

2.116 All patients with variant CJD for whom genetic information is available have the same genotype (methionine homozygous) at codon 129 position on the PrP gene. This does not mean that other genotypes are not susceptible. Indeed, patients with other genotypes have been infected with CJD following treatment with contaminated growth hormone[48].

Conclusions

2.117 The role of genetic susceptibility in the transmission of CJD between people is unclear. Until the role of genetics is better understood, it is prudent to assume that everyone is susceptible to transmission from CJD, although the incubation period may vary.

Summary of infectivity of blood components and surgical instruments

2.118 The risks from blood components and plasma derivatives are unknown. However, should blood be infective, the risk from blood components could be on a par with that from surgical instruments. This is because the quantity of a blood component used to treat patients is much larger than the traces of tissue transferred to patients from contaminated surgical instruments. This means that even relatively low infectivity levels may be of concern. Table 9 compares the possible infectivity transmitted to patients following surgery with the provisional estimates for that following treatment with blood components (variant CJD only).

Table 9 Comparison of possible infectivity of blood components and surgical instruments

Source tissues and tissues exposed during surgery (all CJD)	**Possible infectivity transferred to next patient per procedure [1]**
CNS to CNS, or optic nerve/retina to optic nerve/retina (last 40% of incubation period)	20 ID_{50}
Other eye tissues to other eye tissues (last 40% of incubation period) or lymhpoid tissue to lymphoid tissue for whole duration of infection	0.2 ID_{50}
Blood components (Variant CJD Only) - whole duration of infection	**Possible infectivity per unit**
whole blood, plasma, white cells + platelets, red cells, cryoprecipitate	Possibly zero, but estimates for different components range from 0.01 - 900 ID_{50}[2]
plasma derivatives	Depends on production details and treatment regime but could be up to 1 ID_{50} per dose

[1] Assuming an infectivity of 10^8 ID_{50} /g for CNS and back of the eye to similar tissues; an infectivity of 10^6 ID_{50} /g for other eye tissues and lymphoid tissue to similar tissues; 10 mg

initial load per instrument; 20 instruments per procedure; 10^5-fold decrease in infectivity by decontamination and a 10% transfer of residual infectivity to the subsequent patient

[2]. See Table 7

Clinical procedures categorisation by risk

2.119 This document categorizes clinical procedures according to their likely risk of transmission of prion proteins. In sporadic CJD, only CNS and the eye pose a major risk. These categories are summarized in Table 10.

Table 10 Clinical procedures - categorisation by possible risk[a]

High risk procedures
All procedures that involve piercing the dura, or contact with cranial ganglia (including the trigeminal ganglion) and dorsal root ganglia, or the pineal and pituitary glands.
Procedures involving the optic nerve and retina.
Treatment with blood components. **Variant CJD only**
Medium risk procedures
Other procedures involving the eye, including the conjunctiva, cornea, sclera and iris or the olfactory epithelium.
Procedures involving contact with lymphoid tissue. **Variant CJD only**
Anaesthetic procedures that involve contact with lymphoid tissue during tonsil surgery (for example laryngeal masks). **Variant CJD only**
In certain instances only, to be assessed for each batch of product, treatment with high doses of specific immunoglobulins, normal immunoglobulin, antithrombin and certain clotting factors. **Variant CJD only**
Low risk procedures
All other invasive procedures including other anaesthetic procedures.
Treatment with any blood component or product. **Sporadic CJD**
Treatment with albumin. **Variant CJD only**

[a] Applies to both sporadic and variant CJD unless otherwise stated

Section 3: Public health investigation of incidents

3.1 This section describes the role of the local health teams and the CJD Incidents Panel in investigating incidents that involve invasive medical procedures. The investigation of incidents involving blood donations is covered in Section 5. Advice on the investigation of incidents involving tissue and organ donation will be added at a later date.

3.2 In England, the responsibility for protecting the population from communicable disease now rests with the Primary Care Trusts, with Strategic Health Authorities or Boards having a performance monitoring role. In England, the Consultant in Communicable Disease Control (CCDC), based in either a local health protection team or NHS Trust, will usually lead the local incident team, working closely with the relevant PCT and acute NHS Trust. In Scotland, Wales and Northern Ireland, the appropriate consultant in public health medicine will take this responsibility (CPHM).

3.3 In all incidents, the CCDC/CPHM should contact the secretariat to the CJD Incidents Panel.

Identifying possible exposures to CJD in healthcare settings

3.4 The National CJD Surveillance Unit (NCJDSU) collects, manages and analyses information on all suspect cases of CJD in the UK. Suspect cases are referred to the NCJDSU by clinicians. A neurologist from the unit then visits each case and assigns them to a diagnostic category.

3.5 The clinician caring for the patient should inform the CCDC/CPHM about all possible, probable and confirmed cases of sporadic and variant CJD. This reporting system is described in recent guidance prepared by the NCJDSU, the Public Health Medicine Environmental Group and the UK Health Departments[49].

3.6 The CCDC/CPHM is responsible for co-ordinating the initial response to this information including contacting the Department of Health's CJD Incidents Panel.

3.7 Should other local professionals become aware of a possible incident, they should contact the local CCDC/CPHM who will liaise with the NCJDSU and the Incidents Panel.

Initial information collection

3.8 The CCDC/CPHM should gather the initial information on the case so that the Incidents Panel can assess the need for immediate action. The CCDC/CPHM should use the reporting form in **Annex 3** to collect information on the clinical status of the patient with CJD and the invasive medical procedures carried out on this patient.

3.9 The CCDC/CPHM or their equivalents from all parts of the UK should swiftly inform the secretariat to the CJD Incidents Panel about incidents and also send a copy of the notification to the medical officer in their respective Health Department with responsibility for CJD.

3.10 The contact point for the Incidents Panel is:

Dr Nicky Connor
Consultant Epidemiologist
Medical Secretary to the CJD Incidents Panel
CJD Team
Health Protection Agency Communicable Disease Surveillance Centre (CDSC)
Telephone: GRO-C
Fax: 020 8200 7876
E-mail: nicky.connor@ GRO-C

Initial appraisal and control measures

3.11 The CJD Incidents Panel will rapidly appraise the information on the reporting form, and decide:

either

that there is no significant risk to other patients and no further action is required.

or

that there may be a risk to other patients and that the potentially contaminated instruments should be removed from use (quarantined). This should be carried out following the ACDP/SEAC Guidance[3]. The CJD Incidents Panel will advise on what additional information is required to assess the risk to other patients.

Further information to characterise risk

3.12 Where further investigation is required, the CCDC/CPHM may set up a local incident management team. The CJD Team at CDSC may assist with any risk characterisation exercise, particularly when more than one health authority is involved. This arrangement also pertains to Scotland, Wales and Northern Ireland.

3.13 The team should collect detailed information about the surgical instruments used on the patient with CJD and the patients who may have been exposed to each instrument (Table 11). This information should be presented to the Incidents Panel so that the potential risks may be assessed and managed.

Table 11 Further information required to characterise risk

Instruments
Description of instruments including name, make, size, function and any identifying number.
Standards of documentation of use and decontamination of instruments.
Details of subsequent use of the instruments.
Number of times the instruments have been reused.
Details of decontamination procedures.
Date of removal if the instruments have been removed from clinical use.
Information on whether the instruments have remained in the same set.
If use and decontamination of instruments are not documented, information will also be required on:
Number of instruments in use at the time of the index patient's procedure.
Number of procedures for which they are normally used prior to being discarded because of normal wear and tear.
Number and type of procedures for which these instruments are used in a given time period.
Possibly exposed patients
Number of patients definitely and possibly exposed to the instruments.
Details of how they are identified as being definitely or possibly exposed.
Date, location and type of procedures in which instruments were definitely or possibly used.
Tissues to which the instruments would have been exposed during these procedures.

Risk assessment

3.14 The Incidents Panel will assess the risk of exposure to CJD to subsequent patients by reviewing the data collected by the local incident team. In each case the Panel will consider the clinical condition of the patient, the type of instruments used, the decontamination processes in place and whether the instruments can be traced.

Section 4: Public health management of surgical incidents

4.1 While the risk of transmitting TSEs through invasive medical procedures is uncertain, precautionary action should be taken to prevent the possible transmission of infection. It is also important to collect information about possible exposures to TSEs so that the risk of transmitting TSEs can be better understood. It is important to ensure that actions taken to protect the public health do not prejudice individual patient care.

4.2 The Incidents Panel will advise the local Incident Management Team on the action required to manage incidents involving possible exposure to TSEs in healthcare settings. These actions have four main aims:

- To prevent transmission of TSEs from potentially contaminated instruments.
- To prevent further transmission of TSEs through healthcare from exposed patients who are considered to have a significant risk of having contracted TSEs.
- To collect information on people who could have been exposed to further our understanding of the risk of transmitting TSEs in healthcare settings.
- To inform the public about a local incident.

4.3 The Incidents Panel will use the algorithm in **Annex 4** to help make decisions on managing possibly exposed patients and instruments. The decision points in the algorithm are not automatic, and multiple factors will need to be considered for each case.

Instruments

4.4 In most circumstances, instruments used on the index patient will already have been re-used many times by the time the patient is diagnosed. It follows that most of the risk associated with these instruments will have already occurred.

4.5 Nevertheless, there are grounds for a strongly precautionary approach toward instruments, withdrawing all those that *might* pose a risk whilst the risk is evaluated. Where it is necessary to permanently remove instruments from clinical use, these can provide a valuable resource for research and hospitals will be advised on how to make arrangements for collection.

4.6 In general, instruments that have undergone **ten or fewer decontamination cycles** since being used on the index patient with CJD should be permanently removed from use.

4.7 The Panel may advise that particular instruments are removed from use even if they have undergone more than 10 decontamination cycles. This may be because they are difficult to clean, or because they cannot be mechanically washed or autoclaved.

4.8 The question has arisen whether possibly contaminated instruments could be put through ten cycles of decontamination and then returned to use, safe in the knowledge that they had been effectively decontaminated. We do not believe that this is an appropriate course of action. Currently we have no means of assessing the actual level of contamination on instruments so the decisions about withdrawal are informed by calculations in a mathematical model based on estimates of likely infectivity, amount of infective material adhering to instruments, amount removed by decontamination and so on (see Section 2). These give estimates of the probability that the subsequent use of an instrument may result in the transmission of CJD to the person on whom it was used. Thus rewashing an instrument ten or any other number of times could never be said to guarantee the safety of that instrument for future use. Indeed, depending on the details of the incident, the Panel may suggest the removal of instruments that have already undergone more than ten washes (see previous paragraph). Withdrawal of *all* instruments, no matter how many times they have been re-used and however low the estimated risk, is the only way to eliminate the risk of further transmission completely. This would probably result in some cases in having to stop surgery due to lack of instruments and this could have serious consequences for people needing surgery. We consider the balance struck in this framework is a reasonable balance and gives a proportionate response to the risks.

4.9 If instrument tracing systems are inadequate, it may not be possible to identify the instruments used on the index patient with CJD. In these cases, **any** instrument that may have been used on the index patient, and is not known to have undergone at least 10 decontamination cycles might have to be removed from use.

People with a 'contactable risk' of CJD

4.10 While the risk of transmitting CJD through invasive medical procedures is very uncertain, the modelling set out in figures 2-5 in Section 2 shows that some patients are likely to be at a higher risk than others. The modelling indicates that patients who have undergone procedures with instruments that have only undergone a small number of cycles of use and decontamination since being used on tissues infective for CJD, will be at a greater risk of becoming infected than other exposed patients.

4.11 Patients who have been inadvertently infected with the agent of CJD could pose a risk to others. Therefore patients who may be at risk should be contacted and informed about their possible exposure and its implications. This is in order to protect public health by advising potentially exposed individuals not to donate blood, organs or tissues. The CCDC/CPHM leading the incident investigation will provide details of the potential exposure to the clinician, usually the general practitioner,

who can ensure that appropriate precautions are taken in the event of future medical interventions. The clinician who is responsible for this must also ensure that the confidentiality of the information is maintained and that it is not used for any purpose (for instance in relation to the provision of financial services to the patient) other than the protection of public health. It may be considered that more than one medical adviser should be informed. The choice of the appropriate clinician may be discussed with the individual, who should also be encouraged to share the responsibility for public health protection. The individual would be advised to inform any healthcare professionals (for example in private clinics) who may not otherwise receive this information. The CCDC/CPHM will also inform the UK Blood Service and the various organ and tissue banks. The CCDC/CPHM will ensure that details of patients in this group are recorded on the confidential database (see paragraphs 4.18-4.26).

4.12 The CJD Incidents Panel will advise the Incident Management Team on how many people, if any, should be included in this 'contactable' group **[Annex 4].** The size of this group will depend on the infectivity of the source tissues in the 'index' patient with CJD [Table 12].

Table 12 Patients to be included in 'contactable' group

Clinical procedure in index patient[iii]	**'Contactable' group**
High risk procedures CNS, retina, optic nerve procedures in patients with symptoms or within one year of developing symptoms of any type of CJD	First 6 patients
CNS, retina, optic nerve procedures in patients who develop symptoms of any type of CJD more than 1 year later (and in last 40% of incubation period*).	First 4 patients
Medium risk procedures Other eye tissue procedures that might result in contamination with olfactory epithelium in patients who have, or subsequently develop any type of CJD (in last 40% of incubation period*)	First 2 patients
Lymphoid tissue procedures in patients who have, or subsequently develop variant CJD (at any stage in incubation period).	First 2 patients

* In sporadic CJD the mean period of infectivity is assumed to be 20 years prior to the onset of symptoms. In variant CJD the incubation period is assumed to start in 1980.

[iii] See Annex 2 for detailed categorisation of clinical procedures

4.13 If instrument tracing systems are inadequate, it may not be possible to identify these patients with certainty. Decisions on the group to be contacted should then be made by the CJD Incidents Panel on a case-by-case basis but usually only individuals who can be identified as potentially exposed would be contacted. If it is only possible to identify the cohort of patients that includes potentially exposed individuals, entry on to the database (see below) would be considered.

4.14 Particularly sensitive arrangements will be needed for informing patients that they are included in this group. This information will be burdensome and of little overall benefit to the individuals themselves. It might additionally result in practical difficulties (e.g. insurance).

4.15 The CCDC/CPHM should identify the clinician best placed to carry out this task. However a team of experts on the broader aspects of CJD and experienced in discussing its implications, should be developed to actively support those clinicians and share the consultation(s), if appropriate.

4.16 Appointments should be scheduled at such a time and be of sufficient length to allow exploration of issues and concerns. There should be a facility to supplement advice with telephone contact and a further appointment if required. Written material supporting the consultation, to be taken away, will be available, prepared with the assistance of the CJD Incidents Panel.

4.17 Patients will be counselled as to the current incomplete understanding of risk, and requested to collaborate with active follow up by informing whoever manages the database of any changes of address. They should be advised that they may, if they so choose, opt out of inclusion in the confidential database but may not prevent information being passed to the relevant healthcare providers to ensure protection of public health.

People on the database

4.18 In addition to tracing the "contactable group", incident management teams should collect information on other 'possibly exposed' people so that the risk of transmitting CJD through invasive medical procedures can be better understood.

4.19 To this end, a public health database will be maintained at CDSC. This database will include relevant details of exposed individuals from all countries within the UK. The database will enable the long term follow up of people possibly exposed in incidents. The database may also be useful if there are new developments relevant to their health, such as the availability of a drug that prevents the development of sporadic or variant CJD or if new information results in a change in the assessment of the public health risk.

4.20 The CJD Incidents Panel will advise the local team which people should be recorded on this confidential public health database.

4.21 It is important that members of the public are aware of the existence of this database, and realise that they are able to a) find out if they are on the database and b) ask for their records to be altered if incorrect, or deleted (see Public Awareness section).

4.22 In view of the fact that the database may be used to offer individuals drugs should these become available and will be used to develop policies to protect the public against TSE transmission, the Panel hopes that few will opt to remove their details from the database.

4.23 All patients in the 'contactable' group should be included in this database unless they opt out.

4.24 In general, the Panel will advise that the first ten patients operated on with the instruments used for medium or high risk procedures (Table 10) on the index patient with CJD should be entered on this database.

4.25 If instrument tracing systems are inadequate, it may not be possible to identify the patients at risk of exposure. In this case, the group of people who could include the first 10 patients may be entered on the database. The Panel will advise on a case-by-case basis.

4.26 The Panel's work will be helped by the widespread thorough implementation of traceability of surgical instruments.

Section 5: Advice on the investigation and management of incidents involving blood (variant CJD only)

This section has been 'greyed out' while it is being finalised.

Investigation

5.1 The UK Blood Services (UKBS) work with the CJD Surveillance Unit to identify blood donations from people who later are found to have developed vCJD.

5.2 If blood from donors who later develop vCJD has been used to produce plasma derivatives, UKBS inform the relevant manufacturer; Bio Products Laboratory for England and Wales, and the Protein Fractionation Centre for Scotland and Northern Ireland.

5.3 The manufacturer can then identify and trace the implicated products. The manufacturer is obliged (CMMP regulations) to notify the incident to the Medicines & Healthcare products Regulatory Agency (MHRA). The MHRA will then advise the manufacturer to recall any implicated products by contacting pharmacy departments, haemophilia centres etc. Where necessary, the MHRA facilitates this process by issuing a 'Drug Alert' to health professionals. In practice, no fractionated products prepared from UK plasma remain in circulation, so recall is not an option, but the fractionators will notify the MHRA of an incident and issue a notification to recipient pharmacy departments, haemophilia centres etc.

5.4 If the products are still within their shelf life the manufacturer is also obliged to inform other companies who have purchased implicated products as ingredients in other medicines or for use in the manufacture of other medicines.

5.5 If implicated products have been sold overseas, the manufacturer should inform their customers and the regulatory authorities. The MHRA will issue a rapid alert to regulatory authorities in other EC member states, and will contact other countries via the WHO.

5.6 Proposals

5.7 When the UKBS become aware of implicated blood donations, they identify any issued blood components and notify the Consultant Haematologist in charge of the blood transfusion laboratory which received those blood components. The haematologist will instigate investigation on the fate of the blood components and identify any recipients.

5.8 When the haematologist has identified the recipients of the blood components, he/she should inform the local CCDC/CPHM for the Trust(s) and the hospital control of infection officer. The CCDC/CPHM should inform the CJD Incidents Panel about the incident. The CCDC/CPHM may also ask CDSC to provide assistance, and help co-ordinate incidents that involve more than one trust.

5.9 The CCDC/CPHM, together with the hospital infection control doctor, should then investigate the incident, identifying the recipients of the blood components.

5.10 The UKBS should inform the CJD Incidents Panel if any implicated blood has been used to manufacture plasma derivatives.

5.11 The UKBS should ask the manufacturers to provide the CJD Incidents Panel with the information required to assess the risks from the plasma derivatives. This should include details of the products issued, their manufacture and the number of plasma donations pooled.

Removal of blood from use

5.12 The UKBS are responsible for ensuring that any implicated blood components that are in date are withdrawn from use.

5.13 The relevant manufacturer is responsible for ensuring that implicated plasma derivatives are withdrawn from use.

Blood components

5.14 While blood has not yet been found to be infective in vCJD, as a precautionary step, recipients of blood components (red cells, platelets, plasma, white cells, cryoprecipitate) donated by someone who goes on to develop vCJD should be included in the contactable group.

5.15 The CCDC/CPHM should ensure that these individuals are informed about their exposure, and receive public health advice. This may be carried out by the patients' GP or other suitable health professional (see Section 4).

5.16 The CCDC/CPHM should also pass information about these individuals to the CJD Incident database at CDSC.

Plasma derivatives

5.17 The risk from plasma derivatives is less clear and the CJD Incidents Panel will need to assess each case individually, using the information supplied by the manufacturer.

5.18 The CJD Incidents Panel may advise contacting recipients of some implicated plasma products where assessment indicates a medium level of risk. For each incident, the CJD Incidents Panel will calculate the total dose of product that would indicate that a patient should be contacted and precautionary measures advised.

5.19 The CJD Incidents Panel may advise that some recipients of plasma derivatives need not be contacted, but where possible, they should be recorded on the CJD incidents database. All such recipients should have the right to find out if they have received the implicated product should they so choose.

Table 13 Patients to be included in 'contactable' group

Blood Product Administered[iv]	
Whole blood, red cells, plasma, platelets	all recipients of components from a donor who went on to develop vCJD
plasma derivatives	recipients of a sufficient dose of the product to have potentially received 0.02 iv ID_{50} vCJD agent

5.20 The CJD Incidents Panel will ask the manufacturers to inform organisations in their distribution chain, including pharmacy departments and haemophilia centres, about the implicated product and the Panels assessment of the risks from each product.

5.21 The CJD Incidents Panel will provide information to the manufacturer for distribution to these organisations. This will explain which doses of products are unlikely to pose a risk to recipients, and will direct the organisation to contact the local CCDC/CPHM(s).

5.22 The CCDC/CPHM will then work with the hospitals and other organisations to identify recipients and collect details of the doses of derivatives that have been given. The CCDC/CPHM will then pass this data on to CDSC for entry onto the database.

5.23 It may not be possible to identify all recipients. For example, albumin is used in a wide variety of medicinal products, and there may be no way of identifying who has received products made from an implicated batch.

5.24 When the Panel advises that recipients should be contacted, the CCDC/CPHM should ensure that these individuals are informed about their status, and that public health advice is given. Where the contactable patients are under the care of a Haemophilia Centre, or an immunodeficiency physician, the clinicians responsible for the patients' care should inform and advise the patients. Given the special relationships built up between the clinician and patient in this context, further support may not be required. However, the Panel proposes that a cadre of experts is established to support local teams communicating information on the risks of CJD from surgical procedures and the same cadre of experts should also be able to assist clinicians dealing with blood-related incidents. For contactable patients who are not under the care of a Haemophilia centre or an immunodeficiency physician, another health professional (e.g. GP) may be the most appropriate clinician to inform and support the patient. In these cases assistance from the cadre of experts may then be required (see Section 4).

[iv] See Annex 2 for detailed categorisation of clinical procedures

Section 6: Public awareness

Principles

6.1 Principles of public openness underlie this guidance:-

6.2 Information about TSEs should be widely available. This should include information on the current knowledge of the risk of contracting TSEs through medical procedures and the actions being taken to improve knowledge and minimise these risks.

6.3 Members of the public have a right to know about specific incidents and if they could have been exposed to a potential risk. Concerned individuals who wish to find out about possible exposure should be advised that there is currently no test to find out whether someone is incubating a TSE and no cure for the disease.

6.4 Health teams should try to avoid informing people about possible risk-exposure against their will. The only exception to this is where there is a need to take action to protect the public health. In these cases, the potentially exposed individual would always be informed, as well as the Blood Service, tissue and organ banks. The individual concerned should be made fully aware that this confidential process of notification is taking place and consulted over the identification of the appropriate health professional, usually the patient's General Practitioner. He/she should also be advised of the need to inform a medical adviser to ensure that other health professionals who may be involved in future surgical or dental care can be alerted in confidence. The medical adviser would normally be the general practitioner but some may elect to nominate another doctor (eg a consultant within a haemophilia unit). The individual should also be encouraged to share the responsibility for protecting public health by informing healthcare providers (for instance in a private clinic) who might not receive this information from the nominated medical adviser(s).

6.5 A database of possibly exposed patients will be set up to help to determine the risk of transmitting TSEs through invasive medical procedures. Patients have a right to decide whether their personal information is kept on this database. Systems should be set up to allow patients to exercise this right without necessarily having to find out about their own exposure status.

Objectives

6.6 Following on from this, the public communication has six main objectives:-

- To provide general information on TSEs, the current knowledge of the risk of contracting TSE through medical procedures and actions being taken to improve our knowledge and minimise these risks.
- To provide general information about particular incidents.
- To provide an opportunity for individuals to discuss, clarify and obtain reassurance about any of this.

- To provide a mechanism for individuals who remain concerned to find out if they were possibly exposed and to receive appropriate local care and support.
- To provide information to concerned individuals about the current lack of a diagnostic test and cure for TSEs.
- To provide a mechanism for individuals to remove themselves from the database of exposed individuals without needing to find out if they were exposed.

National information

6.7 The public should have access to information about TSEs, what is known about the risk of transmitting TSEs through invasive medical procedures, how the Department of Health is responding to this situation and the need for further research.

6.8 The public should be informed through publicity material including leaflets and posters that are made widely available in healthcare settings. A media campaign would also be effective in informing members of the public.

6.9 Additional information should be available on recognised health websites.

6.10 Further information and support may be provided by **NHS Direct**. In Scotland, a similar service is provided by NHS24. Support during incidents should be arranged locally following the principles described in this document.

Local information in an incident

6.11 The public should have access to information on particular incidents. This should:-

- Reiterate the general information outlined above.
- Provide specific information about the incident.
- Provide reassurance where possible.
- Explain the purpose, value and mechanism of the database of exposed people.
- Advertise a means for individuals who remain especially concerned to discuss or clarify any issues.
- Enable individuals who still remain especially concerned to be removed from the database and/or to find out whether they were exposed.

6.12 This would be done in the following ways:-

- A press release which refers to the general information leaflet and websites as sources of information (see above).
- These information sources also advertise that individuals who remain concerned can ring NHS Direct (NHS24 in Scotland) to discuss the issues involved.

Information for concerned individuals

6.13 Individuals who ring NHS Direct speak initially to a Health Information Adviser who notes the caller's demographic details and that this call is related to clinical exposure to TSEs. There are then two possible options:-

6.14 The concerns are addressed by this Health Information Adviser using a flowchart and question and answer sheets.

6.15 The call is passed to one of a smaller group of Health Information Advisers who are experienced in this field. They would also use the flow chart and question and answer sheets to address the caller's concerns.

6.16 The Helpline should meet the Commission for Health Improvement standards[50]. Help lines in Scotland relating to specific incidents will be established and managed by NHS24.

Bibliography

[1] Risk assessment for Transmission of variant CJD via surgical instruments: A modelling approach and numerical scenarios. Economics and Operational Research Division Department of Health, December 2000, London. http://www.doh.gov.uk/cjd/riskassessmentsi.htm

[2] Det Norske Veritas (DNV) 'Assessment of the risk of exposure to variant CJD infectivity in blood and blood products' Final report for Department of Health, February 2003.

[3] The Advisory Committee on Dangerous Pathogens (ACDP) and the Spongiform Encephalopathy Advisory Committee (SEAC) Joint Working Group 'Transmissible Spongiform Encephalopathy Agents: Safe Working and the Prevention of Infection', 1998. http://www.official-documents.co.uk/document/doh/spongifm/report.htm

[4] Advisory Committee on the Microbiological Safety of Blood and Tissues for Transplantation MSBT. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation. Department of Health August 2000. http://www.doh.gov.uk/msbt/msbt.pdf

[5] Bruce ME, *et al.,* Detection of variant CJD infectivity in extraneural tissues. The Lancet: 2001; 358: 208-209.

[6] Kimberlin RH & Walker CA. Pathogenesis of experimental scrapie: dynamics of agent replication in spleen, spinal cord and brain after infection by different routes, Journal of Comparative Pathology 1979; 89: 551-562

[7] Diringer H, Braig HR. Infectivity of unconventional viruses in dura mater. The Lancet 1989; 1: 439-40

[8] Kimberlin RH & Walker CA. Pathogenesis of scrapie in mice after intragastric infection. Virus Res 1989; 12: 213-220

[9] Wadsworth JDF, *et al.* Tissue distribution of protease resistant prion protein in variant Creutzfeldt-Jakob disease using a highly sensitive immunoblotting assay. The Lancet 2001; 358:: 171-80.

[10] Head MW *et al* Prion accumulation in eyes of patients with sporadic and variant Creutzfeldt-Jakob disease 2003; 44: 342-6

[11] Hogan RN *et al.* Replication of scrapie protein in hamster eyes precedes retinal degeneration. Ophthalmic Res 1986; 18: 230-5

[12] Marsh RF, Hanson RP. Transmissible mink encephalopathy: infectivity of corneal epithelium. Science.1975 ;21;187(4177):656.

[13] Kimberlin RH & Walker CA. Pathogenesis of experimental scrapie. In: Novel Infectious Agents and the Central Nervous System Ciba Foundation Symposium No 135, Edited by G Bock and J Marsh, 1988 pp 37-62. Wiley, Chichester

[14] Zanusso G, Ferrari S, Cardone F, Zampieri P, Gelati M, Fiorini M, Farinazza A, Gardiman M, Cavallaro T, Bentivoglio M, Righetti PG, Pocchiari M, Rizzuto N, Monaco S. Detection of pathologic prion protein in the olfactory epithelium in sporadic CJD. NEJM 2003; 348:711-719

[15] Hilton DA *et al.* Prion immunoreactivity in appendix before clinical onset of variant CJD. The Lancet 1998; 352: 703 –704.

[16] Hilton DA *et al.* Accumulation of prion proetin in tonsil and appendix: review of tissue samples. British Medical Journal 2002; 325: 633-634.

[17] Hill AF *et al.* Investigation of variant CJD and other human prion diseases with tonsil biopsy samples. The Lancet 1999; 353: 183-189.

[18] Hadlow *et al.* Natural infection of Suffolk sheep with scrapie virus. Journal of Infectious Diseases 1982;146, 5: 657-664

[19] Ironside JW, *et al* Pathological diagnosis of variant Creutzfeldt-Jakob disease. APMIS 2002; 110: 79-87.

[20] Ward HJT, *et al.* Variant Creutzfeldt-Jakob disease. Clinics in Laboratory Medicine 2002 (in press).

[21] Head M W, Ritchie D, McLoughlin V, Ironside J I. Investigation of PrPres in dental tissues in variant CJD British Dental Journal (in press).

[22] Ingrosso L, Pisani F, Pocchiari M. Transmission of the 263K scrapie agent by the dental route. Journal of General Virology 1999; 80: 3043-3047

[23] Adams DH, Edgar WM Transmission of agent of Creutzfeldt-Jakob Disease. British Medical Journal 1978; 1: 987.

[24] Carp RI. Transmission of scrapie by the oral route: Effect of Gingival Scarification. The Lancet 1982; 170-171

[25] Kimberlin RH, Wilesmith JW. Bovine spongiform encephalopathy (BSE): epidemiology, low dose exposure and risks. In: Slow infections of the central nervous system: Edited by J Bjornsson, RI Carp, A Love and HM Wisniewski. Annals of the New York Academy of Sciences. 1994; 724: 210-220

[26] Fraser J R. Infectivity in extraneural tissues following intraocular scrapie infection. Journal of General Virology 1996; 77: 2663-2668

[27] Taylor DM, Fraser JR The potential risk of transmitting variant CJD through surgery. Journal of Hospital Infection 2000; 44: 318-321

[28] Goodbrand *et al.* Prion protein accumulation in the spinal cords of patients with sporadic and growth hormone associated CJD. Neuroscience Letters. 1995; 183: 127-130

[29] Brown P, Gibbs Jr CJ, *et al.* Human Spongiform Encephalopathy. The National Institutes of Health series of 300 cases of experimentally transmitted disease. Ann Neurology 1994; 35: 513-529

[30] Brown P, *et al.* Iatrogenic Creutzfeldt-Jakob Disease at the millenium Neurology 2000; 55: 1075-1081

[31] Manuelidis *et al.* Experimental CJD transmitted via the eye with infected cornea. New England Journal of Medicine 1977; 1334-1337

[32] Tateishi J. Transmission of CJD from human blood and urine into mice. The Lancet 1988; 2: 1074

[33] Heckmann JG *et al.* Transmission of CJD via corneal transplant. J Neurology, Neurosurgery and Psychiatry 1997; 63: 388-90

[34] Duffy P *et al* Possible person to person transmission of Creutzfeldt-Jakob Disease. New England Journal of Medicine 1974; 290: 692-3

[35] Blanquet-Grossard F, *et al.* Prion protein not detectable in dental pulp from patients with Creutzfeldt-Jakob Disease. J Dent Res. 2000; 79 (2): 700

[36] Chen SG *et al.* Effect of consecutive treatments of STERIS TM on protease-resistant prion protein contaminated devices in vitro (poster). Abstracts of 3rd NMHCC Conference on TSEs, San Diego. 16-17 March 1998

[37] Verjat D *et al.* Fluorescence-assay on traces of protein on re-usable medical devices: cleaning efficiency. Int. J. Pharm. 1999; 179: 267-271.

[38] Taylor DM Inactivation of prions by physical and chemical means J. Hosp. Infection 1999; 43 (Supplement) S69-S76.

[39] Taylor DM Inactivation of transmissible degenerative encephalopathy agents: A Review Veterinary Journal 2000; 159: 10-17.

[40] Fleschig E, *et al* Transmission of scrapie by steel-surface-bound prions. Molecular Medicine 2001 7 679-684

[41] http://www.show.scot.nhs.uk/sehd/publications/sspr/sspr.pdf

[42] Controls Assurance www.doh.gov.uk/riskman.htm

[43] Independent Health Care National Minimum Standards Regulations Act 2000. Stationary Office.

[44] Risk Assessment for vCJD and Dentistry. Economics and Operational Research Division, Department of Health 2003 http://www.doh.gov.uk/cjd/dentistryrisk/index.htm

[45] Lee CA, *et al.,* Retrospective neuropathological review of prion disease in UK haemophilia patients. Thrombosis and Haemostasis 1998; 80: 909-11

[46] Hunter N, *et al* Transmission of prion diseases by blood transfusion. J.Gen.Virol. 2002; 83 (Part 11): 2897-905

[47] Brown P, *et al.* The distribution of infectivity in blood components and plasma derivatives in experimental models of transmissible spongiform encephalopathy. Transfusion 1998; 38: 810-816

[48] Brandel JP, Preece M. et al. Distribution of codon 129 genotype in human growth hormone treated CJD patients in France and the UK. Lancet 2003: 362 (9378): 128-30

[49] Guidance on local reporting by clinicians of Creutzfeldt-Jacob Disease and local action by Consultants in Communicable Disease Control. November 2003 www.cjd.ed.ac.uk/guidance.htm

[50] Commission for Health Improvement Discussion Paper "Guidelines for the NHS in establishing and running help lines. 2002 www.chi.nhs.uk

Annex 1 Advice and policy on reducing the risk of CJD through medical procedures

Rigorous implementation of washing, decontamination and general hygiene procedures is key in minimising the risk of transmitting CJD on surgical instruments. This is the advice from SEAC which has been incorporated into several sets of advice from the Department of Health to the NHS.

Health Service Circular (HSC) 1999/179 emphasises the importance of implementing existing guidance on the cleaning & sterilisation of medical devices[1]. It is complemented by a CD-ROM titled *Decontamination Guidance,* which draws together existing guidance on decontamination of medical equipment.

Health Service Circular HSC 2000/032 requires NHS organisations to review their management arrangements urgently and to carry out a health and safety audit of their decontamination procedures[2].

Systems that can track instrument sets through decontamination and use on patients are vital in identifying which instruments are used on a particular patient. Health Service Circular HSC 2000/032 also instructs Trusts to set up such systems.

In addition to advising on the importance of effective decontamination, SEAC also advised that the use of single use instruments should be considered where practicable, provided patient safety is not compromised.

This advice is reiterated in HSC 1999/178. This describes the actions that health organisations and clinicians should take to reduce the risk of transmission[3].

Following the advice from SEAC, the Department of Health introduced single-use instruments for tonsil surgery [4]. This decision was reversed in December 2001 in England, following concerns over adverse events associated with the single use instruments[5]. Northern Ireland did not experience adverse events, but has largely returned to reusable instruments. Single use instruments remain the standard recommendation for routine tonsillectomy in Scotland.

The Advisory Committee on Dangerous Pathogens (ACDP) advises government on health and safety risks from infectious diseases. A SEAC/ACDP Joint Working Group has been set up to advise on health and safety risks arising from CJD. This committee has issued advice on the measures to be taken when surgical interventions are carried out on patients with known or suspected CJD, or in one of the 'at risk' categories (3). This includes advice on the use and disposal of surgical instruments.

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[1] Health Service Circular (HSC) 1999/179 *"Controls Assurance in Infection Control: Decontamination of Medical Devices"*

[2] Health Service Circular (HSC) 2000/032 *"Decontamination of medical devices"*

[3] Health Service Circular (HSC) 1999/178 *"Variant Creutzfeldt-Jakob Disease (vCJD) : Minimising The Risk Of Transmission"*

[4] Department of Health Announcement 04 January 2001

[5] Department of Health Announcement 14 December 2001

The Joint Working Group guidance considers the following groups to be potentially 'at risk' of developing CJD: recipients of hormone derived from human pituitary glands e.g. growth hormone, gonadotrophin, recipients of dura mater grafts, people with a family history of CJD, i.e. close blood line relatives (parents, brothers, sisters, children, grandpartents and grandchildren).

Three precautionary measures have been taken to reduce any potential risk of transmitting CJD through blood. First, people at risk of developing CJD are excluded from donating blood. Second, since April 1999, all major blood products (e.g. Factor VIII, immunoglobulins and anti-D for Rhesus negative pregnant women) have been manufactured from plasma donated outside the UK. Third, since October 1999 blood donated in the UK has been processed to remove its white blood cells (leucodepletion).

Annex 2 Instrument construction

The large majority of surgical instruments are manufactured from stainless steel. This can vary in quality (there are over 60 types of steel). Major European and USA manufacturers usually use high quality steel, but instruments of other origin may be made from lower grade steel which is difficult to clean effectively.

The finish on an instrument can be polished or matt, and matt finished devices are more difficult to clean. Other materials such as aluminium, titanium and plastics can be part or the whole of an instrument structure. Aluminium and plastic are more difficult to clean than high grade stainless steel. Titanium devices should clean easily. Construction of devices varies from simple "single surface" to complex, multi-jointed or multi-part construction.

The following categorisation of instruments may help in considering how easily cleanable a particular instrument might be. Expert advice should be sought on instruments where the category is not clear.

Instrument category	**Examples of instruments**
Category A: Can be decontaminated[6]	
Single-surface, no working parts	Macdonalds dissector, Deaver retractor
Jointed smooth jaws and no ratchet	Sinus forceps/scissors
Jointed with serrated jaws and ratchet	Spencer-Wells artery forceps
Multi-part instrument that can be dismantled into component parts	Balfour retractor
Category B: Varying degree of decontamination possible	
Multi-part/jointed instrument that cannot be fully dismantled	Compound action bone rongeur
Instruments with lumen	Minimal invasive surgery kit
Category C: Impossible to guarantee safe decontamination[7]	
Power tools(air or electric driven), not machine washable	Maxi-driver, Hall saw
Exotic kit with multi-part, multi-material, only partly strippable	Stereotactic neuro set
Fibre optic flexible scopes	
Instruments with lumen	neuro brain canula

[6] If made from poor quality steel instruments may not be effectively decontaminated.
[7] Some well-constructed kit in this category may be possible to decontaminate

Annex 3: Reporting form for possible exposures to CJD through medical procedures

Please use this form to report a CJD Incident to the Panel secretariat.
Please send it to:

Dr Nicky Connor
Consultant Epidemiologist
Medical Secretary to the CJD Incidents Panel
CJD Team
Health Protection Agency Communicable Disease Surveillance Centre
61 Colindale Avenue
London NW9 5EQ

Tel: GRO-C
Fax: 020 8300 7868
e-mail: nicky.connor@ GRO-C

CJD Incident Reporting Form

CDSC contacted date:	CDSC staff member taking call:		**PI**

Informant Name: .....

Position:

Organisation: Address:

.....

Telephone:

Fax: .....

E-mail

CCDC/CPHM informed Yes/No. If 'No', advise caller to inform local CCDC/CPHM

CCDC/CPHM Name:

Address:

Telephone number:

email address:

Index patient:

Age: DOB:

CJD diagnosis	at risk	possible	probable	confirmed
sporadic				
variant				
familial				
iatrogenic				

Date of onset of symptoms	
Date of first presentation to clinician	
Current state of patient/ Date of Death	

NCJDSU informed	
NCJDSU reference number	
If not confirmed, please give supporting details	
Possibility of making a firmer diagnosis?	
Who made the diagnosis (NCJDSU, local neurologist etc.)	
Other comments:	

Incident details (please use a new page for each procedure) **Procedure number:**	
Date of procedure	
Description of procedure	
Tissues involved CNS / Dental / Eye / Gingiva / LRS / Other	If other, please specify:
Name of hospital or other healthcare setting	
Anaesthetic procedures	
Description type and number of used instruments	
What cleaning/disinfectant/sterilisation procedures would they have undergone?	
Place of cleaning/disinfection/sterilisation	
Follow up logistics	
Possibility of tracing of used instruments	
Current whereabouts of instruments	
How many people might have been exposed to the used instruments (or pool of instruments)?	
Action taken	
Quarantine of instruments	
Formation of local incident team, and decisions made	
Media preparation	
Other	

Incident details (please use a new page for each procedure) **Procedure number:**						
Date of procedure						
Description of procedure						
Tissues involved						If other, please specify:
CNS	Dental	Eye	Gingiva	LRS	Other	
Name of hospital or other healthcare setting						
Anaesthetic procedures						
Description type and number of used instruments						
What cleaning/disinfectant/sterilisation procedures would they have undergone?						
Place of disinfection/sterilisation						
Follow up logistics						
Possibility of tracing of used instruments						
Current whereabouts of instruments						
How many people might have been exposed to the used instruments (or pool of instruments)?						
Action taken						
Quarantine of instruments						
Formation of local incident team, and decisions made						
Media preparation						
Other						

Annex 4: CJD Incident: Decision Management

CCDC/CPHM leads the investigation (Box 1)

↓

What type of CJD does the index patient have? (Box 2)

↓

Did the medical procedure involve high, medium or low risk tissues? (Box 3)

↓

At what stage of the incubation period was the procedure carried out? (Box 4)

↓

ACTIONS (Box 5)
Instruments/devices
Patients
Information

Box 1: Who to involve

Local investigation team:
Hospital infection control team, trust management, appropriate clinical team, theatre team, CSSD, press office.

Others:
CJD Incidents Panel Secretariat (contact at CDSC)
CDSC CJD Team
Regional Epidemiologist
National CJD Surveillance Unit

Box 2: CJD Diagnosis

How has the National CJD Surveillance Unit classified the patient?
Does the patient have a confirmed/probable diagnosis of Sporadic or Familial CJD?
If not, what is the CJD classification?
Has an alternative, non-CJD diagnosis been made?

Box 3: Risk level of tissue

Incidents only include procedures that involve contact with mucous membranes or skin penetration.
Were high or medium risk tissues involved?
For confirmed/probable sporadic/familial CJD these include CNS, eye and olfactory epithelium. This includes front of eye procedures such as tonometry.
For other CJD classifications where variant CJD is a possibility, these also include lymphoid tissue (tonsil, spleen, appendix, colon, adrenal glands, lymph nodes). This includes endoscopies and bronchoscopies.

Box 4: Stage of incubation

For high or medium risk tissues in confirmed/probable sporadic/familial CJD:
Infectivity is present while symptoms are present, and in the last 8 years of the incubation period.
For other CJD classifications where variant CJD is a possibility:
Lymphoid tissue – infectivity may be present at any time from 1980.
Other medium/high risk tissues – infectivity may be present while symptoms present and in the last 40% of the incubation period (assume infected in 1980)

Box 5: Actions

Instruments: Quarantine if contact with medium or high risk tissues, if infectivity was present at time of procedure. Panel will advise on future use of instruments/devices.
Contacting patients: How precisely can the first 6 patients on whom the instruments were subsequently used be identified? The Panel will advise on whether any patients should be contacted.
The local team should retain all incident information.

Glossary

ACDP	Advisory Committee on Dangerous Pathogens, established in 1981 to advise the Health and Safety Executive on all aspects of hazards and risks to workers and others from exposure to pathogens.
BSE	Bovine Spongiform Encephalopathy, a slowly progressive and ultimately fatal neurological disorder of adult cattle transmitted by contaminated animal feed.
CDSC	Communicable Disease Surveillance Centre. Responsible for monitoring human infectious diseases.
CJD	Creutzfeldt-Jakob Disease, a human transmissible spongiform encephalopathy that can occur in sporadic, familial and acquired (iatrogenic) forms.
Cleaning	A process which physically removes contamination but does not necessarily destroy micro-organisms.
CNS	Central nervous system. This includes the brain, cranial nerves and spinal cord.
Contactable Patients	People exposed in an incident who are are considered to have a higher risk of acquiring CJD. They should be contacted and informed about their exposure so that action may be taken to prevent any further spread of disease.
CSF	Cerebrospinal fluid, the fluid that bathes the brain and spinal cord.
Decontamination	A process which removes or destroys contamination and thereby prevents micro-organisms or other contaminants reaching a susceptible site in sufficient quantities to initiate infection or any other harmful response.
Definite case of CJD	An international definition used by the CJD Surveillance Unit that refers to the diagnostic status of cases. In definite cases the diagnosis will have been pathologically confirmed, in most cases by post mortem examination of brain tissue (rarely it may be possible to establish a definite diagnosis by brain biopsy while the patient is still alive).
Dose response relationship	This describes how the amount of an infectious agent affects the likelihood that an exposed individual becomes infected.

Dura mater	The outermost and strongest of the three membranes (meninges) which envelop the brain and spinal cord.
Endoscopes	Tube-shaped instruments inserted into a cavity in the body to investigate and treat disorders. There are many types of endoscopes e.g. arthroscopes, laparoscopes, cyctoscopes, gastroscopes, colonoscopes and bronchoscopes.
Familial CJD	CJD cases that occur in families, associated with mutations in the PrP gene (10 - 15% of all CJD cases).
HGH	Human growth Hormone. At one time made from pituitaries from human cadavers. This was rarely contaminated with CJD agent, and is now known to have transmitted CJD to a number of those treated with hGH for short stature.
Iatrogenic CJD	Infection with CJD that occurred as the result of a medical procedure. Recent UK cases have resulted from treatment with human derived pituitary growth hormones or from grafts using dura mater (a membrane lining the skull).
Lymphoreticular system (LRS)	Lymphoreticular System is referred to because of its possible infectivity in variant CJD. Infectivity has been demonstrated in the lymph nodes, appendiceal lymphatic tissue, spleen and tonsils in variant CJD.
Median infective dose (ID_{50})	The statistically derived single dose of a infective agent that can be expected to cause infection in 50 per cent of a given population of organisms under a defined set of experimental conditions.

Medical device	An instrument, apparatus, appliance, material or other article, whether used alone or in combination together with any accessories or software necessary for its proper functioning, intended by the manufacturer to be used for human beings in the: *diagnosis, prevention, monitoring, treatment or alleviation of disease or injury; investigation, replacement or modification of the anatomy or of a physiological process; control of conception;* and which does not achieve its principal intended action by pharmacological, chemical, immunological or metabolic means, but which may be assisted in its function by such means.
NCJDSU	The National CJD Surveillance Unit was established in Edinburgh in 1990, to identify and study all cases of CJD in the UK.
Possible case of CJD	An international definition used by the CJD Surveillance Unit that refers to the diagnostic status of cases. Possible cases fulfil certain clinical criteria, but do not meet the criteria for probable or definite cases.
Prion	PROteinaceous INfectious agent. The prion theory suggests that the infective agent of CJD (and the other TSEs) is only composed of a protein and does not contain nucleic acid which would be necessary if the agent was a conventional virus.
Prion protein (PrP)	Protease-resistant membrane protein, also known as prion protein (PrP): a normal, host-coded protein that becomes protease-resistant in infected tissue and accumulates around CNS lesions in TSEs. Until recently, the function of PrP was unknown despite its presence in many different organs and tissues of healthy animals, including the brain. There is recent evidence that PrP in uninfected animals has the property of mopping up harmful 'oxygen free radicals' or carries out some signalling functions between cells.
Probable case of CJD	An international definition used by the CJD Surveillance Unit that refers to the diagnostic status of cases. Probable cases fulfil clinical criteria but do not meet the criteria for definite cases.
Prophylactic	Treatments used to prevent infection or disease.
PrP^C	The normal cellular isoform of PrP.
PrP^{Sc}	The abnormal disease-specific isoform of PrP derived post-translationally from PrP^C. PrP^{Sc} is a generic term now used for all disease-associated PrP.
PrP-res	
Scrapie	A TSE endemic in British sheep and found in many parts of the world. It is also found in goats. Scrapie can be transmitted naturally or experimentally to other animals such as mice and

	this provides an experimental model for work on TSEs.
SEAC	Spongiform Encephalopathy Advisory Committee. This was established in April 1990 to advise government on matters related to Spongiform Encephalopathies.
Single Use Device	Any device deemed unsuitable by the manufacturer for re-processing.
Sporadic CJD	Cases of CJD that occur at random throughout the world and have no known cause. This is the commonest form of CJD.
TME	Transmissible mink encephalopathy. This is a TSE of minks that has been found in mink farms in the USA, probably resulting from dietary exposure to scrapie.
Transmissible Spongiform Encephalopathy (TSE)	Transmissible spongiform encephalopathy. Fatal diseases of the neurological system characterised by spongy degeneration of the brain with progressive dementia. Examples include CJD in humans, and scrapie and BSE in animals
Variant CJD	Identified in 1996 as a previously unrecognised form of CJD, having a novel pathology and consistent disease pattern. Exposure to BSE is the most likely explanation for the emergence of the disease. It was previously known as nvCJD (new variant CJD).