Annex B

Diagnostic criteria

B1. Paragraphs 4.17 and 4.18 in Part 4 of this guidance, including Table 4a**,** categorise CJD patients in descending order of risk, distinguishing between *symptomatic* and *asymptomatic* patients. *Symptomatic* patients are those who fulfil the internationally accepted diagnostic criteria, set out below, for *definite*, *probable* and *possible* CJD or vCJD (http://www.cjd.ed.ac.uk/criteria.htm).

B2. Suspect cases are classified according to these criteria by a neurologist from the National CJD Surveillance Unit (NCJDSU), on an on-going basis. The classification is recorded at 4 "key" stages:

- at notification;
- when the patient was first seen, in life, by a neurologist from the NCJDSU;
- the highest classification on the sole basis of clinical information (i.e. not including neuropathological information);
- when a NCJDSU review is completed (i.e. when the case-file is closed). The completed case file may, or may not, include neuropathological data

B3. The date of any change of classification and the reason for such a change is recorded as necessary in the NCJDSU.

Classification criteria

Sporadic CJD

B4. Neuropathological/immunocytochemical confirmation is required for a diagnosis of definite sporadic CJD.

B5. *Probable* sporadic CJD patients will have rapidly progressive dementia, **and at least two** of the following four symptoms:

a) myoclonus
b) visual or cerebellar problems
c) pyramidal or extrapyramidal features
d) akinetic mutism

plus typical electroencephalogram (EEG) with generalised triphasic periodic complexes at approximately 1 per second,

or clinical criteria for *possible* sporadic CJD (see below) **and** a positive assay for 14-3-3 protein in the cerebrospinal fluid (CSF).

B6. *Possible* sporadic CJD patients will have rapidly progressive dementia, **two** of the symptoms listed in paragraph B5(a)-(d) above **and** a duration of less than 2 years.

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Iatrogenic (accidentally transmitted) CJD

B7. *Definite* iatrogenic CJD requires a neuropathological diagnosis of CJD in a patient with a recognised risk factor for iatrogenic CJD (see Box B1).

Probable iatrogenic CJD is defined as either a progressive predominantly cerebellar syndrome in a human pituitary growth hormone recipient, **or** a clinical diagnosis of probable CJD (see definition in paragraph B5 above) in a patient with a recognised risk factor for iatrogenic CJD (see Box B1)

Box B1

RELEVANT EXPOSURE RISKS FOR THE CLASSIFICATION AS IATROGENIC CJD

The relevance of any exposure to disease causation must take into account the timing of the exposure in relation to disease onset

- Treatment with human pituitary growth hormone, human pituitary gonadotrophin or human dura mater graft
- Corneal graft in which the corneal donor has been classified as definite or probable human prion disease
- Exposure to neurosurgical instruments previously used in a case of definite or probable human prion disease
- Transfusion of blood from a donor subsequently diagnosed with vCJD

This list is provisional as previously unrecognised mechanisms of human prion disease may occur

Genetic TSE

B8. *Definite* genetic TSE requires a neuropathological confirmation of TSE, **plus either** *definite* TSE in a first degree relative (i.e. a parent, child or sibling), **or** a pathogenic prion protein gene (*PRNP*) mutation (see Box B2).

Probable genetic TSE is defined as a progressive neuropsychiatric disorder **plus** either *definite* or *probable* TSE in a first degree relative, **or** a pathogenic *PRNP* mutation (see Box B2).

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Box B2

***PRNP* MUTATIONS ASSOCIATED WITH GSS* NEUROPATHOLOGICAL PHENOTYPE**

P102L, P105L, A117V, G131V, F198S, D202N, Q212P, Q217R, M232T, 192 bpi

***PRNP* MUTATIONS ASSOCIATED WITH CJD NEUROPATHOLOGICAL PHENOTYPE**

D178N-129V, V180I, V180I+M232R, T183A, T188A, E196K, E200K, V203I, R208H, V210I, E211Q, M232R, 96 bpi, 120 bpi, 144 bpi, 168 bpi, 48 bp*del*

***PRNP* MUTATIONS ASSOCIATED WITH FFI** NEUROPATHOLOGICAL PHENOTYPE**

D178N-129M

***PRNP* MUTATION ASSOCIATED WITH VASCULAR PrP AMYLOID**

Y145s

***PRNP* MUTATIONS ASSOCIATED WITH PROVEN BUT UNCLASSIFIED PRION DISEASE**

H187R, 216 bpi

***PRNP* MUTATIONS ASSOCIATED WITH NEURO-PSYCHIATRIC DISORDER, BUT NOT PROVEN PRION DISEASE**

I138M, G142S, Q160S, T188K, M232R, 24 bpi, 48 bpi, 48 bpi + nucleotide substitution in other octapeptides

*GSS – Gertmann-Straussler-Scheinker disease
**FFI – Fatal Familial Insomnia

variant CJD (vCJD)

B9. *Definite* vCJD patients will have a progressive neuropsychiatric disorder **and** neuropathological confirmation of the disease, showing spongiform change and extensive PrP^{Sc} deposition with florid plaques throughout the cerebrum and cellebellum.

B10. *Probable* vCJD patients can be classified under two sets of criteria:

(I) They will have progressive neuropsychiatric disorder of a duration greater than 6 months, where routine investigations do not suggest an alternative diagnosis. They will also have **at least four** of the following five symptoms:

a) early psychiatric symptoms (depression, anxiety, apathy withdrawal, delusions)
b) persistent painful sensory symptoms (including both frank pain and/or unpleasant dysaesthesia)
c) ataxia
d) myoclonus or chorea or dystonia
e) dementia

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An EEG will not show the typical appearances of sporadic CJD, **or** no EEG has been performed and there is a symmetrical high signal in the posterior thalamus on a MRI brain scan ([1] Zeidler et al 2000).

These patients would have had no history of potential iatrogenic exposure and no evidence of a familial form of TSE.

(II) Alternatively, a *probable* vCJD patient will have had a progressive neuropsychiatric disorder for a period of longer than six months, where routine investigations do not support an alternative diagnosis, and where there is no history of potential of iatrogenic exposure or evidence of a familial form of TSE, **plus** a tonsil biopsy which is positive for PrP^{Sc}.

B11. *Possible* vCJD patients will have progressive neuropsychiatric disorder of a duration greater than 6 months, where routine investigations do not suggest an alternative diagnosis, and there is no history of potential iatrogenic exposure or evidence of a familial form of TSE. They will **also** have **at least four** out of five of the symptoms listed in paragraph B10 (I) (a)-(e) above **and** an EEG that does not show the typical appearance of sporadic CJD **or** no EEG has been performed.

Patients who do not fulfil the criteria for possible CJD

B12. The NCJDSU have designated three additional categories for patients who are referred to the Unit but who do not meet the criteria for *possible* CJD. These can be summarised as:

(i) **Diagnosis unclear** – the diagnostic criteria for *definite*, *probable* or *possible* CJD are not met, nor is there a reasonable alternative diagnosis. CJD therefore remains a possibility;

(ii) **CJD thought unlikely** – information indicates that a clinical diagnosis of CJD is very unlikely because of atypical disease features, and/or an atypical course, and/or atypical clinical investigation results, and/or a reasonable alternative diagnosis is made but is <u>not</u> confirmed. This category includes cases which recover clinically without a firm alternative diagnosis;

(iii) **definitely not CJD** – information indicates that CJD is <u>not</u> the diagnosis and there is an alternative definite diagnosis proven on the basis of clinical examination, clinical investigations or pathology.

[1] Zeidler M, Sellar RJ, Collie DA, Knight R, Stewart G, Macleod MA, Ironside JW, Cousens S, Colchester AC, Hadley DM, Will RG. The pulvinar sign on magnetic imaging in variant Creutzfeldt-Jakob Disease. Lancet. 2000; **355:** 1412-8

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