Dear Colleague

Re: Surveillance of vCJD-DOH funded UKHCDO study

As you are aware, Professor Christine Lee, on behalf of the TTI Working Party, has obtained Department of Health funding for a UKHCDO vCJD surveillance study of haemophilia (and other bleeding disorder) patients.
We know that some of our patients have been exposed to products that contained donations from individuals who subsequently developed vCJD. All UK residents, including people with haemophilia, may have also been exposed to this risk in the 1980s and 1990s through the food chain. For this reason, it is important that the study contains those exposed to implicated batches (see attached). Those who have not been exposed to implicated UK factor concentrates will also be included in the study and will constitute an important control group.

The study will have the following components (for details refer to attached information):
1. Collection of data on those exposed to implicated batches throughout the UK.
2. Notification of any confirmed clinical cases.
3. Prospective study of tissues taken at operation.
4. Prospective study of postmortem material.
5. Retrospective study of postmortem and biopsy material.

It is proposed that the data will be collected and collated through the UKHCDO and the data stored in the National Haemophilia Database. The patient leaflet about the database is currently with the printers. All patients need to be provided with this information. The Haemophilia Society, Haemophilia Nurses Association and UKHCDO informed the CJD Incident panel that it was preferable for these data to be collected on the National Haemophilia Database than on the proposed separate national database recording vCJD exposures/incidents.

This is obviously a very important study for the UK haemophilia population and I hope you will participate. If you wish to discuss any aspect more fully then please contact myself or Professor Christine Lee.

Yours sincerely

Professor Frank Hill
Chairman, UKHCDO
Department of Clinical & Laboratory Haematology
The Birmingham Children's Hospital
Steelhouse Lane
Birmingham
B4 6NH

APPENDICES

I. **National Haemophilia Database Patient Information Leaflet**

II. **Notification form**

III. **General information sheet**

IV. **BMJ article 2002: First hundred cases of variant Creutzfeldt-Jakob disease: retrospective case note review of early psychiatric and neurological features.** *Spencer et al: 324 (7352): 1479*

http://bmj.com/cgi/reprint/324/7352/1479.pdf

V. **Notification of Negative Results of Investigations in Suspected Cases of vCJD**

VI. **Consent form for prospective analysis of pathological specimen.**

VII. **Letter to GP**

VIII. **Form when patient declines consent for vCJD biopsy analysis**

IX. **Post-mortem consent form for next-of-kin**

X. **Consent form for retrospective analysis of pathological specimen.**

XI. **Copy of MREC approval letters dated 10/09/01 and 25/02/03**

XII. **Sample LREC letter**

Chairman: Dr. F. G. H. Hill, Department of Clinical & Laboratory Haematology, The Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH
Tel: GRO-C Fax: GRO-C Email: frank.hill@ GRO-C

Vice-Chairman: Dr. C. R. M. Hay, University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL
Tel: GRO-C Fax: GRO-C Email: chay@ GRO-C

Treasurer: Dr. G. Dolan, Department of Haematology, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH
Tel: GRO-C Fax: GRO-C Email: gerry.dolan@ GRO-C

Secretary: Dr. R. F. Stevens, Department of Haematology, Royal Manchester Children's Hospital, Pendlebury, Nr. Manchester M27 1HA
Tel: GRO-C Fax: GRO-C Email: Richard.Stevens@ GRO-C

Registered Charity No. 1032606

UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

UKHCDO/DOH vCJD SURVEILLANCE **Appendix II**

Notification of Patients who have received at risk products

Send to: Ms Lynne Dewhurst, UKHCDO National Haemophilia Database Co-ordinator, University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.
Tel: GRO-C Fax: GRO-C

NOTES:
1. THIS FORM SHOULD BE COMPLETED REGARDLESS OF WHETHER PATIENT HAS BEEN INFORMED.
2. THIS INFORMATION IS **STRICTLY CONFIDENTIAL** AND WILL BE STORED ANONYMOUSLY.
3. PLEASE COMPLETE AS FULLY AS POSSIBLE

UKHCDO National Registration Number of Patient: .....

Date of Birth: .....

Date of Death (where relevant): .....

Diagnosis: .....

Relevant Batch Number(s):.....

Total Quantity Used (of each batch): .....

Number of Treatment Episodes:.....

Dates Given (start and final date): .....

Name and Number of Haemophilia Centre:.....

Name of Consultant: .....

History of: (please fill in as appropriate or mark X if no history)
1. Neurosurgery: ..... Date: .....
2. Tonsillectomy:..... Date: .....
3. Appendicectomy:..... Date: .....
4. Treatment with Growth Hormone: ..... Date: .....

Any other information: .....

Date: .....

A copy of this form should be filed in the patient's notes

UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

vCJD General Information Sheet **Appendix III**

Recently there has been a lot of media interest surrounding vCJD, which has led to conflicting and confusing facts and information being given.
The aim of this information sheet is to explain what we know about this disease, and, in particular, whether it is possible that it can be transmitted by blood or plasma products.

What is vCJD?
Variant Creutzfeldt-Jakob disease is a rare and fatal human neurodegenerative condition. Like Creutzfeldt-Jakob disease (CJD), vCJD is classified as a transmissible spongiform encephalopathy (TSE) because of characteristic spongy changes in the brain and its ability to be transmitted. TSEs are also known as prion diseases. vCJD is a new form of prion disease which was first described in 1996.
Before the identification of vCJD, CJD was recognised to exist in only three forms. The first, known as 'sporadic', has an unknown cause and accounts for around 90% of CJD cases. The second form is called 'iatrogenic' and results from the accidental transmission of the causative agent via contaminated surgical equipment, various brain or eye operations or growth hormone injections. The remaining cases are inherited.

What causes vCJD?
vCJD is strongly linked with exposure to the Bovine Spongiform Encephalopathy (BSE) agent. BSE is a TSE affecting cattle and was first reported in the UK in 1986. An epidemic followed but the number of cases of BSE has gradually fallen since 1992. It is not clear exactly how BSE originated, nor how it was spread amongst cattle. BSE has since been reported in other countries.

How is it transmitted?
It is most likely that the spread from cattle to humans was by food and although consuming particular meat products (e.g. hamburgers, sausages) has been suggested, there is, at present, no definitive evidence that eating any particular foodstuffs increases the chances of getting vCJD. We therefore do not know exactly how humans became infected with BSE.

Is vCJD a virus similar to, for example, hepatitis?
No. The exact nature of the infectious agent causing vCJD is not known and this has made detection of it (e.g. by blood testing) very difficult.

How many people have been diagnosed with vCJD?
Since 1996, 129 cases of vCJD have been diagnosed in the UK, 1 in Ireland and six in France to date. Although the BSE epidemic in the UK is now under control, it is not known either how many humans may have been affected or the time delay before symptoms of vCJD develop (incubation period). All these unknown factors make it extremely difficult to predict how many more people will develop vCJD.

Who gets vCJD?
So far, the majority of cases have been diagnosed in young adults, with an average age of 26 years. The reasons for this are not clear. There is no difference between the sexes. The number of cases in the north of the UK is higher than the south; it is not known why this is. No clear dietary link has been established. All of the vCJD cases diagnosed so far have been found to have part of a particular gene in common; however it is likely that this gene (which is found in one quarter to one third of the population), merely speeds up the time between acquiring the infection and developing symptoms of

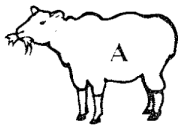
vCJD (incubation period). Experts do not feel that testing individuals for this gene type would be helpful.
It is likely that a combination of factors, at present unknown, put particular individuals at increased risk of developing vCJD.

What are the symptoms of vCJD?
There are several symptoms common to vCJD patients. These include rather vague initial symptoms of depression, confusion and personality and behavioral changes. As the disease advances the patient experiences a rapidly progressing dementia and uncontrolled jerking movements known as myoclonus. Problems develop with language, sight, muscle weakness and co-ordination. The patient becomes rigid and in the final stages of disease loses all mental and physical functions. The duration of vCJD from the onset of symptoms to death is, on average one year.

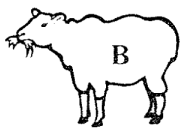
How is vCJD diagnosed?
vCJD has been found in the tonsils and in the brain and confirming a diagnosis requires taking small samples of one of these tissues. A variety of other investigations, such as lumbar puncture, brain scanning (MRI) and looking at the pattern of brain waves (EEG), may assist in making the diagnosis.

Can vCJD be transmitted by blood or plasma product transfusions?
There is no evidence that the classical (sporadic) form of CJD is transmitted by blood or blood product transfusions. However, because vCJD is a relatively 'new' disease, insufficient information has been collected to be absolutely certain about such transmission. Some experiments have shown that vCJD can affect some of the cells of the immune system which are found in blood (special types of white blood cells). This has led to various safety measures (see below) being taken as a precaution against any possible spread by blood. Reassuringly, patients with vCJD have not received more blood transfusions than people without vCJD.
Concern has heightened recently that the risk may be more than theoretical following the discovery of BSE in a sheep that had received a blood transfusion from another sheep who had been fed cow brain infected with BSE. (*see diagram*) The sheep from whom the blood was taken (sheep A) went on to develop BSE later, but had shown no signs of disease at the time the blood was taken for transfusion. This tells us that, even though the sheep was incubating the disease and had no symptoms or signs of disease, it was still able to pass on the disease via a blood transfusion. We have no evidence as yet that the same thing happens in humans who are incubating vCJD.

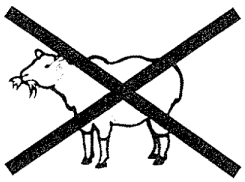
1. Sheep A fed BSE brain



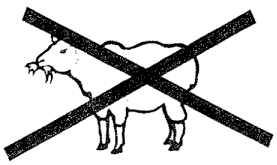
2. Several months later, blood taken and transfused to sheep B



3. Sheep B develops BSE



4. One year after the blood transfusion, sheep A also develops disease



Clotting factor concentrates are prepared from the pooled plasma of several thousand blood donations and experiments have shown that the process by which the clotting factor is made (fractionation) reduces any possible infectivity to virtually zero. Thus, even if it were shown that vCJD could be transmitted by **blood**, the risk of it being transmitted by **clotting factors** would be small. Furthermore, many donations go into each plasma pool to make the clotting factors and therefore it is also possible that any infected plasma donation would be diluted significantly, thus reducing the risk of transmission. There have been no cases of vCJD in patients with haemophilia.

In summary, there is no evidence that blood or plasma products transmit vCJD in humans, but, because some risks exist, both theoretical and from the sheep experiments, measures have been taken to further improve safety.

What measures have been taken to improve the safety of clotting concentrates?

1. Since 1998, all plasma used to make clotting factors in the UK has been imported from the USA where there have been no cases of BSE or vCJD; Scotland also imports some plasma from Germany.
2. Recombinant clotting factors are to be preferred to plasma derived concentrates. In the UK, since 1997, all haemophilic patients under the age of 16 have received recombinant products. This provision has recently been extended to adult patients in Scotland and Wales, but not yet England and Northern Ireland
3. All blood and blood products in the UK are now specially filtered to reduce the numbers of cells in the blood that may be implicated in the transmission of vCJD. This filtering process is called leucodepletion.

And in monitoring patients with haemophilia?

There have been three BPL recalls and one SNBTS recall of blood product batches to date. This was a precautionary measure taken when it was found that one of the donors of the plasma pool had later developed vCJD. At the time of the recalls, the batches had past their expiry date, so the vast majority of these clotting factors would have already been given to patients.

As new cases of vCJD are diagnosed, it is possible that further recalls will occur if the patient has previously donated blood. It is very important that surveillance of haemophilic patients, including those who have received such batches, takes place. This will provide vital information which will help us understand more about the safety of plasma products.

A confidential database, which runs alongside the UK National Haemophilia Database in Manchester, has been set up for this purpose by the Department of Health in conjunction with the United Kingdom Haemophilia Centre Doctor's Organisation (UKHCDO). Information is anonymous and this exercise is being undertaken solely for monitoring and observational purposes.

Is there a blood test available to detect vCJD?

Not yet. Scientists are working very hard trying to develop some form of test which could detect vCJD, but it is unlikely that this will be available in the near future.

Is there a treatment or cure for vCJD?

No. Many drugs are being looked at, but at present, there is no treatment or cure.

How would I know if I had vCJD?

Nobody knows what the risks are of acquiring vCJD and we have no idea how many people are incubating the disease. Because no test is currently available, we have no way of finding out who has vCJD before clinical symptoms develop. Given that the incubation period may be very long, even if a test showed that an individual was incubating the disease, it may not be possible to tell when, if at all, symptoms may develop.

If I have received clotting factor from one of the recalled batches, am I at risk of 'carrying' vCJD and therefore passing it on to others?

Because of the theoretical risks of vCJD transmission by blood and blood products, the question arises of risk of transmission to others. Particular procedures or operations such as having tonsils removed may put patients being operated on the same list at risk. The size of risk is totally unknown and at present it is not clear what should be done in such circumstances. The surgeon performing the procedure should be made aware and discuss the specific case with the doctor who is responsible for the care of the haemophilic patient.

FURTHER INFORMATION

www.cjdfoundation.org
www.cjd.ed.ac.uk

Dr Carolyn Millar
Clinical Co-ordinator
UKHCDO/DOH vCJD Surveillance
January 2003

UKHCDO/DOH vCJD SURVEILLANCE **Appendix V**

Notification of Negative Results of Investigations in Suspected Cases of vCJD

The following patient *: ....., date of birth: .....

has been investigated for vCJD and all results have been negative.
(* UKHCDO National Registration Number)

The investigations performed were as follows:

.....

.....

These were performed in view of the following symptoms:

.....

.....

The patient had/had not received implicated batches of factor concentrate.
If the answer to the above is 'yes', please indicate batch number below:

Year of Recall	Product Name	Batch Number	Date of Issue
1997	Factor VIII 8Y	FHB 4419	9/08/95-14/09/95
	Factor VIII 8Y	FHB 4547	6/12/96-20/01/97
	Replenate	FHE 4548	28/10/96-22/11/96
2000	Factor VIII 8Y	FHB 4596	13/05/97-13/08/97
	Replenate	FHD 4579	8/03/97-15/07/98
	Replenate	FHE 4536	11/09/96-8/10/96
	Replenate	FHE 4579	25/02/97-8/01/98
	Replenate	FHF 4577	10/02/97-20/03/97
	Replenine-VF	FJM 4596	30/04/97-19/05/97
1987-1989			
SNBTS recall	Factor VIII Z8	0301-70320	
		0304-70510	
	Factor IX DEFIX	3502-70210	
		3506-70250	

Signed: .....

Name:.....(BLOCK CAPITALS)

Date: .....

Send to: Ms Lynne Dewhurst, UKHCDO National Haemophilia Database Co-ordinator, University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL.

UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

UKHCDO/DOH vCJD SURVEILLANCE

Appendix VI
Version 3:4/07/01

CONSENT FORM

FOR PROSPECTIVE ANALYSIS OF PATHOLOGICAL SPECIMEN

There have been concerns that blood and/or blood products might be capable of transmitting variant Creutzfeldt-Jakob disease (vCJD), the human form of BSE, to humans. However, at the present time there is no evidence that blood products can transmit vCJD and world wide there have been no cases of vCJD in individuals with haemophilia. The Department of Health has considered it important to manage prospective and retrospective surveillance in haemophilic patients within the UK and have provided funding for that purpose. This surveillance is to be co-ordinated through the UK Haemophilia Centre Doctors' Organization (UKHCDO), which already holds a Confidential National Haemophilia Database and information about this is enclosed. Specimens would be sent to the specialised laboratory of the National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh and any results obtained would be given to you in person by your own haemophilia doctor.

We would like to request your permission to send a specimen of your/your child's

.....

to be removed at operation, to Edinburgh for analysis for vCJD.

I agree for a specimen of my/my child's.....

to be sent for analysis at the National Creutzfeldt-Jakob Disease Surveillance in Edinburgh.

I would/ would not want to be informed of the result.

Signed: ..... Date: .....

Name: .....(PLEASE PRINT)

To be filed in patient's notes

Chairman: Dr. F G H Hill, Department of Clinical & Laboratory Haematology, The Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH
Tel: GRO-C Fax: GRO-C Email: frank.hill@ GRO-C

Vice Chairman: Dr. C R M Hay, University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL
Tel: GRO-C Fax: GRO-C Email: chay@ GRO-C

Treasurer: Dr. G Dolan, Department of Haematology, University Hospital, Queen's Medical Centre, Nottingham, NG7 2UH
Tel: GRO-C Fax: GRO-C Email: gerry.dolan@ GRO-C

Secretary: Dr R E Stevens, Department of Haematology, Royal Manchester Children's Hospital, Pendlebury Nr. Manchester, M27 1HA
Tel: GRO-C Fax: GRO-C Email: Richard.Stevens@ GRO-C

Registered Charity No: 1032606

UKHCDO/DOH vCJD SURVEILLANCE

Appendix VII
Version 1:12/00

LETTER TO GP

Dear Dr

There have been concerns that blood and/or blood products might be capable of transmitting Creutzfeldt-Jakob disease, although no epidemiological evidence for this exists in the United Kingdom. In 1996, the CJD Surveillance Unit in Edinburgh described a new variant form of CJD (vCJD) in a series of 10 patients with clinical and neuropathological features which were unusual for classical sporadic CJD.

In 1998 in the UK there were 4979 patients with haemophilia A, 1099 patients with haemophilia B and 5259 patients with von Willebrand's disease registered at the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) database in Manchester. Many of these individuals will have received treatment with blood products, including clotting factor concentrates and therefore, may be at risk of infection with CJD or vCJD. A confidential database has been set up in order to manage both prospective and retrospective surveillance in these patients.

Your patient.....has agreed today to have specimens sent to the National CJD Surveillance Unit in Edinburgh for analysis under the direction of Professor James W. Ironside, Reader in Pathology.

Yours sincerely

UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

UKHCDO/DOH vCJD SURVEILLANCE

Appendix VIII

DECLINE of CONSENT

FOR PROSPECTIVE ANALYSIS OF PATHOLOGICAL SPECIMEN

There have been concerns that blood and/or blood products might be capable of transmitting variant Creutzfeldt-Jakob disease (vCJD), the human form of BSE, to humans. However, at the present time there is no evidence that blood products can transmit vCJD and world wide there have been no cases of vCJD in individuals with haemophilia. The Department of Health has considered it important to manage prospective and retrospective surveillance in haemophilic patients within the UK and have provided funding for that purpose. This surveillance is to be co-ordinated through the UK Haemophilia Centre Doctors' Organization (UKHCDO) which already holds a Confidential National Haemophilia Database and information about this in enclosed.

It is understood that you are undergoing a surgical or diagnostic procedure, but DO NOT wish the tissue biopsies to be examined for vCJD.

I **decline to give consent** for the analysis of.....biopsy specimen for vCJD.

I understand that this form is fully confidential and for monitoring and observational purposes only.

Signed: ..... Date: .....

Send to: **Ms Lynne Dewhurst**
UKHCDO National Haemophilia Database Co-ordinator
University Department of Haematology
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL

UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

UKHCDO/DOH vCJD SURVEILLANCE

Appendix IX
Version 2:5/02/03

CONSENT FROM NEXT-OF-KIN

FOR RESULTS OF POSTMORTEM EXAMINATION
(to be completed in addition to standard hospital post-mortem form)

There have been concerns that blood and/or blood products might be capable of transmitting variant Creutzfeldt-Jakob disease (vCJD), the human form of BSE, to humans. However, at the present time there is no evidence that blood products can transmit vCJD and world wide there have been no cases of vCJD in individuals with haemophilia. The Department of Health has considered it important to manage prospective and retrospective surveillance in haemophilic patients within the UK and has provided funding for that purpose. This surveillance is to be co-ordinated through the UK Haemophilia Centre Doctors' Organization (UKHCDO), which already holds a Confidential National Haemophilia Database and information about this in enclosed.

You have agreed to a postmortem examination to be performed on

.....

As part of this, samples will be sent to the National Creutzfeldt-Jakob Disease Surveillance in Edinburgh where they will be examined for evidence of vCJD.

The results of the postmortem will be available to you.

It is, however, your decision as to whether you wish to be informed specifically of the results of the tests for vCJD:

I do/do not wish to be informed of the result of the tests for vCJD.

Signed: ..... Date: .....

Relationship to deceased: .....

To be filed in patient's notes

Chairman: Dr. F G H Hill, Department of Clinical & Laboratory Haematology, The Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH
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Vice Chairman: Dr. C R M Hay, University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL
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Treasurer: Dr. G Dolan, Department of Haematology, University Hospital, Queen's Medical Centre, Nottingham, NG7 2UH
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Registered Charity No: 1032606

UKHCDO

United Kingdom Haemophilia Centre Doctors' Organisation

UKHCDO/DOH vCJD SURVEILLANCE

Appendix X
Version 1:12/00

CONSENT FORM

FOR RETROSPECTIVE ANALYSIS OF PATHOLOGICAL SPECIMEN

There have been concerns that blood and/or blood products might be capable of transmitting variant Creutzfeldt-Jakob disease (vCJD), the human form of BSE, to humans. However, at the present time there is no evidence that blood products can transmit vCJD and world wide there have been no cases of vCJD in individuals with haemophilia. The Department of Health has considered it important to manage prospective and retrospective surveillance in haemophilic patients within the UK and have provided funding for that purpose.

This surveillance is co-ordinated through the UK Haemophilia Centre Doctors' Organization (UKHCDO). The specialised laboratory services of the National Creutzfeldt-Jakob Disease Surveillance unit in Edinburgh will be used to investigate specimens.

We would like to request your permission to send a specimen of your/your child's:

.....which was removed at operation on

....., to Edinburgh for analysis for vCJD.

I agree for a specimen of my/my child's.....

to be sent for analysis at the National Creutzfeldt-Jakob Disease Surveillance in Edinburgh.

I would/ would not want to be informed of the result.

Signed: ..... Date: .....

To be filed in patient's notes

Chairman: Dr. F.G.H Hill, Department of Clinical & Laboratory Haematology, The Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH
Tel: GRO-C Fax: GRO-C Email: frank.hill@ GRO-C

Vice Chairman: Dr. C.R.M.Hay, University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL
Tel: GRO-C Fax: GRO-C Email: chay@ GRO-C

Treasurer: Dr. G.Dolan, Department of Haematology, University Hospital, Queen's Medical Centre, Nottingham, NG7 2UH
Tel: GRO-C Fax: GRO-C Email: gerry.dolan@ GRO-C

Secretary: Dr R.F.Stevens, Department of Haematology, Royal Manchester Children's Hospital, Pendlebury Nr. Manchester, M27 1HA
Tel: GRO-C Fax: GRO-C Email: Richard.Stevens@ GRO-C

Registered Charity No: 1032606

APPENDIX X1

NHS

The London Multi-Centre Research Ethics Committees

The Old Refectory
Central Middlesex Hospital
Acton Lane
London
NW10 7NS

Tel: GRO-C
Fax:
Email: louise.cox@ GRO-C

10th September 2001
hd/lc/01-11

Professor Christine Lee
Director
Haemophilia Centre & Haemostasis Unit
Royal Free Hospital
Pond Street
London NW3 2QG

Dear Professor Lee

Application reference number: MREC/01/2/11
Title: Surveillance of new variant CJD – UKHCDO

The Chairman of the London Multicentre Research Ethics Committee has considered the amendments submitted in response to the Committee's earlier review of your application on 28th March 2001 as set out in our letter dated 3rd April 2001. The documents approved were as follows:

Letter from Professor Lee *(dated 4th July 2001)*
Letter from Professor Lee *(dated 14th March 2001)*
MREC Application Form *(dated 29th December 2000)*
Protocol *(dated 29th December 2000)*
Patient Information Sheet from the UK Haemophilia Doctors Organisation *(dated 4th July 2001)*
Consent Form for Prospective Analysis of Pathological Specimen *(Version 3, dated 4th July 2001)*
Consent Form for Children for Prospective Analysis of Pathological Specimen *(Version 1, dated 4th July 2001)*
Consent Form for Retrospective Analysis of Pathological Specimen *(Version 1, dated December 2000)*
Consent for Storage of Blood for Future Analysis *(Version 1, dated December 2000)*
Consent for Prospective analysis of Pathological Specimen *(Version 1, dated December 2000)*
Letter to GP *(Version 1, dated December 2000)*
Protocol for the Management of the UKHCDO Database *(Draft, dated 20th December 1999)*
Information regarding Haemophilia Centres (Journal of the Royal College of Physicians of London November / December 1997 Vol. 31, No. 6 pp. 642)
Standard Operating Procedures for the UKHCDO Database *(dated 6th April 2000)*
Principal Researcher's Curriculum Vitae *(dated 27th December 2000)*

The Chairman, acting under delegated authority, is satisfied that these accord with the decision of the Committee and has agreed that there is no objection on ethical grounds to the proposed study. I am, therefore, happy to give you our approval on the understanding that you will follow the conditions of the approval set out below. The project must be started within three years of the date on which MREC approval is given.

While undertaking the review of your application the MREC noted the research involves the establishment of a new disease or patient database for research purposes / the use of an existing database collected for previous research or other purposes with subsequent patient contact patient. **For this reason you are asked to read carefully the sections concerning LREC involvement and local NHS management set out below as there are specific requirement involved when undertaking such research.**

MREC Conditions of Approval

- No research procedures are undertaken until the appropriate local research ethics committees is informed of the research including the name of the local clinician involved.

- The local clinician must inform his/her NHS organisation of their co-operation in the research project.

- The protocol approved by the MREC is followed and any changes to the protocol are undertaken only after MREC approval.

- If projects are approved before funding is received, the MREC must see, and approve, any major changes made by the funding body. The MREC would expect to see a copy of the final questionnaire before it is used.

- You must promptly inform the MREC of:
  (i) any changes that increase the risk to subjects and/or affect significantly the conduct of the research;
  (ii) any new information that may affect adversely the safety or welfare of the subjects or the conduct of the trial.

- You must complete and return to the MREC the annual review form that will be sent to you once a year, and the final report form when your research is completed.

LREC involvement

When undertaking the review of your project the MREC observed that there is/ limited patient contact involving the performance of a technical procedures or additional data collection as described in the MREC approved protocol/ initial contact by a local clinician for purposes of recruitment. It is felt that these tasks appear well within his/her routine professional competence and adequate facilities for such procedure are available as part of his/her normal professional practice.

For this reason you are asked to only inform the appropriate LREC of the project by sending a copy of this letter and also **giving the name and contact details of the local clinician involved and what procedures will be undertaken by this person**. If (unusually) the LREC has any reason to doubt that the local clinician is competent to carry out the tasks required, it will inform the clinician and the MREC that gave ethical approval giving full reasons.

When such tasks are performed by centrally based researchers it should be assumed that the MREC has reviewed their competence to undertake the tasks and it is not necessary to inform the LREC of the contact details but only that the research will take place.

You are not required to wait for confirmation from the LREC before starting your research.

Local NHS Management

The local clinician must inform his/her NHS organisation of their co-operation in the research project and the nature of their involvement. Care should be taken to ensure with the NHS organisation that local indemnity arrangements are adequate.

Legal and Regulatory Requirements

It remains your responsibility to ensure in the subsequent collection, storage or use of data or research sample you are not contravening the legal or regulatory requirements of any part of the UK in which the research material is collected, stored or used. If data is transferred outside the UK you should be aware of the requirements of the Data Protection Act 1998.

ICH GCP Compliance

The MRECs are fully compliant with the International Conference on Harmonisation/Good Clinical Practice (ICH GCP) Guidelines for the Conduct of Trials Involving the Participation of Human Subjects as they relate to the responsibilities, composition, function, operations and records of an Independent Ethics Committee/Independent Review Board. To this end it undertakes to adhere as far as is consistent with its Constitution, to the relevant clauses of the ICH Harmonised Tripartite Guideline for Good Clinical Practice, adopted by the Commission of the European Union on 17 January 1997. The Standing Orders and a Statement of Compliance were included on the computer disk containing the guidelines and application form and are available on request or on the Internet at http://dspace.dial.pipex.com/mrec .

Yours sincerely

GRO-C

Louise Cox
Administrator
The London Multicentre Research Ethics Committee

The London Multi-Centre Research Ethics Committee

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25th February 2003
pw/lc/01-11

Professor Christine Lee
Haemophilia Centre & Haemostasis Unit
Royal Free Hospital
Pond Street
London NW3 2QG

Dear Professor Lee

Application Reference Number **MREC/01/2/11**
Title **Surveillance of new variant CJD – UKHCDO**

Dr Carolyn Millar in her email to the London MREC dated 5th February 2003 attached an amendment relating to the above study.

This is to confirm that the London MREC's Executive Sub-Committee (MREC) at its meeting on Tuesday 25th February 2003, agreed that there is no objection on ethical grounds to the following:

Consent Form for Next-of-Kin *(Version 2, dated 5th February 2003)*

I am therefore happy to give you our approval on the understanding that you will follow the protocol as agreed.

Copies of the amendment and this approval letter should be sent to the relevant local research ethics committees for their information.

Yours sincerely

GRO-C

Louise Cox
Administrator
The London Multicentre Research Ethics Committee

CC Dr Carolyn Millar, Royal Free Hospital

CSH to be emailed.

SAMPLE LETTER TO LREC **Appendix XII**

Date: .....

Dear .....

Re: MREC /01/2/11

Title: Surveillance of new variant CJD-UKHCDO

I would like to inform you of our participation in the aforementioned study. This study has full MREC approval and was approved in accordance with the new guidelines issued by Professor Terry Stacey in November 2000 for research where there is no local researcher.

I enclose copies of the MREC approval letters dated 10th September 2001 and 25th February 2003 for your information.

Yours sincerely

.....

CM/UKHCDO/DOH 20/03/2003