NHS

15 MAY 2006

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10th May 2006

Dr Carolyn Millar
Haemophilia Centre & Haemostasis Unit
Royal Free Hospital
Pond Street
London NW3 1SU

Dear Dr Millar

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

Amendment: As detailed in Notice of Substantial Amendment Form dated 10/04/2006

The above amendment was reviewed at the meeting of the London Multicentre Research Ethics Committee's Sub-Committee held on 4th May 2006.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Notice of Substantial Amendment Form	(dated 10th April 2006)
CV for Professor Frank Hill	(dated 31st January 2006)

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed below:

Dr Timothy Steiner	(Chairman)	Reader in Clinical Physiology
Dr John Keen	(Vice Chairman)	General Practitioner

Research governance approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

NHS

Central Office for Research Ethics Committees (COREC)

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.htm#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.corec.org.uk/applicants/apply/amendments.htm.

Details of Chief Investigator:

Name: Professor Frank Hill

Address:
Department of Clinical & Laboratory Haematology
Birmingham Children's Hospital NHS Trust
Steelhouse Lane
Birmingham
B4 6NH

Telephone: GRO-C

E-mail: Patt.mann@ GRO-C

Fax: GRO-C

Full title of study:	Surveillance of new variant CJD -UKHCDO
Name of main REC:	London MREC
REC reference number:	01/2/11
Date study commenced:	March 2002
Protocol reference *(if applicable)*, current version and date:	Protocol 29/12/2000

Amendment number and date:	2nd amendment, May 2006

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC application form

Yes *No*

If yes, please refer to relevant sections of the REC application in the "summary of changes" below.

(b) Amendment to the protocol

Yes *No*

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

Yes *No*

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?

Yes ***No***

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

The original REC application protocol states the following:

'It is planned to set up a confidential database in order to manage both prospective and retrospective surveillance in these [patients with bleeding disorders who have received treatment with blood products and therefore may be at risk of vCJD infection] patients.' At the time of both this application and the commencement of the study there had been three recalls by Bio Products Laboratory in England and the Scottish National Blood Transfusion

Service (1997, 1999 and 2000) of plasma products, including clotting factor concentrates, which had contained plasma provided by donors who were subsequently found to have vCJD. Therefore the Department of Health funded UK Haemophilia Doctors Organisation (UKHCDO) vCJD surveillance study focussed on tracking the recipients of these clotting factor concentrates and flagging these individuals on the National Haemophilia Database. The patient information leaflet for the National Haemophilia Database from the UKHCDO was circulated to all patients registered with bleeding disorders in the UK [enclosed, 4/07/2001], and patients could, and still can, voluntarily 'opt out' of being registered on the database.

The situation changed in September 2004 when many further clotting factor batches were found to have included plasma derived from donations made by individuals who subsequently developed vCJD. These batches became known as 'implicated'. The CJD Incidents panel examined the potential risks to health from having received implicated plasma products. This risk is on top of the general risk of vCJD to the public from consuming beef and beef products that may have been contaminated by the agent causing bovine spongiform encephalopathy. Batches of factor VIII and factor IX were found to result in a greater than 1% additional potential risk of vCJD. In view of the fact that this possible increased risk of vCJD infection could result in a greater risk of secondary onward transmission of vCJD, public health precautions were taken by the Health Protection Agency (HPA) in England, Wales and Northern Ireland, and the Scottish Centre for Infection and Environmental Health (SCEIH), in association with the Department of Health. It was considered likely that further cases of vCJD would occur in people who previously donated blood and therefore more batches of UK-sourced plasma products could become implicated in the future. Therefore it was decided that all patients with bleeding disorders who had received clotting factors derived from UK-sourced plasma between 1980 and 2001 were considered to be 'at-risk' of vCJD for public health purposes. This time period covers the time at which BSE was thought to have entered the human food chain to the last possible expiry date of any product manufactured in the UK that was sourced from UK donors.

In the public health exercise of September 2004, all patients with bleeding disorders who had been treated with UK-sourced clotting factor concentrates between 1980 and 2001 were contacted [see enclosed vCJD and Plasma Products - Letter to patients with bleeding disorders 20/09/04] and informed of their additional potential risk of vCJD. In addition, they were offered the option of finding out whether or not they had received batches, which, at that time, were known to be implicated. They were informed that their 'at-risk' status would be recorded in the patient's medical notes, both hospital and GP, as well as on the National Haemophilia Database [page 4]. Patients were given the opportunity to discuss the implications of the public health recall exercise and the Patient Reply Sheet that accompanied this letter included obtaining written agreement to the recording of this data on the National Haemophilia Database. [Patient Reply Sheet]. Enclosed with the patient letter was patient information [vCJD and Plasma Products – Information for Patients 07/09/04].

In summary, the institution of HPA/Department of Health public heath precautions in patients with bleeding disorders has resulted in a change in the way data is collected for the surveillance of vCJD in these patients.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Document	*Version*	*Date*
Protocol documents 1 and 2	1	29th December 2000
Patient information sheet from the UK Haemophilia Doctors Organisation		4th July 2001
Variant Creutzfeld-Jakob Disease and Plasma Products: 1. Letter to patients with bleeding disorders 2. Information to patients	1	 20th September 2004 7th September 2004

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: GRO-C

Print name: Dr Carolyn M Millar

Date of submission: 13th May 2006

From the research contract between secretary of state for health and Royal Free Hampstead NHS Trust.

Section 3

SCOPE OF WORK

1 Abstract of the Research

There have been concerns that blood and/or blood products might be capable of transmitting CJD to humans, 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 (nvCJD) in a series of 10 patients with clinical and neuropathological features which were unusual for classical sporadic CJD. In 1997 in the United Kingdom there were 5,393 patients with haemophilia A, 1,152 with haemophilia B and 4,512 with von Willebrand's disease registered at the UKHCDO database in Oxford. 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 nvCJD. It is planned to set up a confidential database, in order to manage both prospective and retrospective surveillance in these patients. The study would include:

1. Notification of clinical case of new variant CJD
2. Prospective study of tissues taken at operation
3. Prospective study of post-mortem material
4. Retrospective study of post-mortem material
5. Retrospective study of tissues taken at operation
6. Prospective study of stored plasma, serum, leucocytes and DNA.

2 Policy Relevance of the Research

The risk of new variant CJD from transfusion of blood and blood products is unknown. Patients with haemophilia in the UK have been exposed to plasma-derived clotting factor products made from many thousands of donations of UK-derived plasma. It has been predicted that the ultimate numbers of cases of new variant CJD in the UK ranges from 75-80,000 and a proportion of these people may well be blood donors. Thus surveillance of the haemophilia population in the UK over a period of time (to accommodate the long incubation time) offers a unique opportunity to establish whether infectivity of new variant CJD occurs by blood product infusion.

5. Policy Relevance of the Research:

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6. Proposed starting date: Immediately Proposed duration: 4 Years Months

7. Total cost: £ 136,524

8. GRO-C (Signature of Applicant)

on behalf of UKHCDO (Date) 17.VI.99

9. I have examined this tender and agree that, if a contract is awarded, the research will be carried out under my general supervision.

GRO-C (Sig

(Na

17.VI.99 (Dat

Professor Christine A Lee MA MD DSc(Med)
FRCP FRCPath
Professor of Haemophilia
Director & Consultant Haematologist
Haemophilia Centre & Haemostasis Unit
Royal Free Hospital
Pond Street
London NW3 2QG
Tel: GRO-C
Fax: GRO-C
E-mail: GRO-C

10. I agree that the gradings and salaries quoted in Analysis of costs Part A are in accordance with the practice and scales applying in this University/Institution; and that any grant awarded will be administered by this University/Institution in accordance with the Department of Health's Conditions of Contract.

GRO-C (Finance Officer qualified to make this statement for the Institution)

M. I. DESAI
FINANCE MANAGER
(GRANTS AND DIVISION)
Royal Free Hampstead NHS TRUST
LONDON NW3. (Name and Address: please print)

(Date) 17/6/99

Form RDD/ARF2

Protocol - document ~

SUMMARY OF PROPOSAL

1. Applicant's Surname(s):	Forename(s):	Title:	Post(s) held - if not permanent, please indicate tenure
Lee	Christine Ann		Professor of Haemophilia Director Haemophilia Centre, Royal Free Hospital Chairman Transfusion Transmitted Working Party, UKHCDO

(Please complete a copy of Appendix 1 for all applicants)

2. Official Address:

The Haemophilia Centre
Royal Free Hospital
Pond Street
London
NW3 2QG

Telephone Number: GRO-C

3. Title of Project: Surveillance of new variant CJD – UKHCDO

4. Abstract of Research: No more than 200 words covering the following topics: aims of project; research subject group; sample size, type and location; methods of working.

There have been concerns that blood and/or blood products might be capable of transmitting CJD to humans, 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 (nvCJD) in a series of 10 patients with clinical and neuropathological features which were unusual for classical sporadic CJD. In 1997 in the United Kingdom there were 5,393 patients with haemophilia A, 1,152 with haemophilia B and 4,512 with von Willebrand's disease registered at the UKHCDO database in Oxford. 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 nvCJD. It is planned to set up a confidential database, in order to manage both prospective and retrospective surveillance in these patients. The study would include:

1 Notification of clinical case of new variant CJD.
2 Prospective study of tissues taken at operation.
3 Prospective study of postmortem material
4 Retrospective study of postmortem material.
5 Retrospective study of tissues taken at operation.
6 Prospective study of stored plasma, serum, leucocytes and DNA.

II. DETAILS OF PROPOSED RESEARCH

Detailed outline of proposed research (see notes attached for further details).

Surveillance of new variant CJD – UKHCDO.

We are seeking funding to establish a confidential database in order to manage prospective and possible retrospective surveillance for new variant CJD in patients with haemophilia, who have been treated with clotting factor concentrates. It is envisaged that this would be managed by an administrator and would use the specialised laboratory services of Dr James Ironside, Senior Lecturer in Pathology at the National CJD Surveillance Unit in Edinburgh. There would be close co-ordination with the UKHCDO through the Chairman of the Transfusion Transmitted Infections Working Party of the Executive Committee and the Secretariat. Advice regarding ethics/consent would be given by Professor Doyle at the Royal London Hospital, who has previously advised UKHCDO.

1 Clinical cases of new variant CJD

A description of the clinical condition has already been circulated to all UK Haemophilia Centre Directors and it is expected that anyone suspecting such a case will contact Dr Will at the CJD Surveillance Unit. This Unit has doctors available who can visit individual patients, if necessary, and the arrangement is on a physician to physician referral basis and remains confidential between those two individuals. However, it is anticipated that any haemophilia centre director would also informally tell the Chairman of UKHCDO about the patient and the progression of the investigation.

2 Prospective study of tissues taken at operation

A specifically designed consent form would be used to obtain permission from the patient and to obtain from the patient, knowledge of whether he/she wished to know the results of the findings. It is felt to be inappropriate to take tissues at operation that were not designed to be taken – in particular, it is thought to be unethical to take lymph node biopsies at the time of operation. Histology will be performed locally and appropriate specimens will be referred to the CJD Unit for specialist examination.

3 Prospective study of postmortem material,

Lymphoid tissue, lymph nodes, spleen, appendix and brains of postmortem material will be sent to the CJD Unit in Edinburgh for specialised analyses. It is felt that the normal hospital consent for postmortem should cover this, although it would be necessary to get consent from relatives as to whether they wished to know the information obtained at postmortem.

4 Retrospective study of postmortem material

There has already been pilot study examining the brains of patients who had died from haemophilia centres in Edinburgh, Oxford and London. (Lee et al *Thromb Haemost* 1998; 80: 909-11) There will be a further ascertainment as whether there are more postmortem brains and/or other tissues, in particular, lymphoid tissues available for further study.

5 Retrospective study of tissues taken at operation (living patients)

A review of the availability of specimens such as appendix, which have been removed since the 1980s in patients who are now living and who were treated with clotting factor concentrates will be conducted. These tissues will be sent to the CJD Unit in Edinburgh. This study would not be possible to do anonymously and consent will be obtained from the living patient for such an examination and whether the individual wanted to know the results or not.

6 Examination of histological material

It is expected that normal routine histology will be performed in local hospitals, but the tissue referred to the CJD Unit in Edinburgh will be examined specifically for new variant CJD, in particular, using a monoclonal antibody. Dr James Ironside will be responsible for these tests.

7 Prospective study of stored serum, plasma, leucocytes and DNA

Storage of these specimens will be set up progressively for all patients with haemophilia with their consent.