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Surveillance for asymptomatic carriage of abnormal prion protein in primary immunodeficiency patients
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National CJD Research & Surveillance Unit Surveillance for Asymptomatic Carriage of Abnormal Prion Protein in Primary Immunodeficiency Patients Exposed to UK-Sourced Immunoglobulin

PRION SURVEILLANCE IN PRIMARY IMMUNODEFICIENCY PATIENTS: STUDY PROTOCOL

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Document history

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ACRONYMS

ACDP	Advisory Committee for Dangerous Pathogens
BPL	Bio-Products Laboratory
BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt-Jakob Disease
ESID	European Society for Immunodeficiencies
GP	General Practitioner
NCJDRSU	National CJD Research & Surveillance Unit
NIBSC	National Institute for Biological Standards and Control
NHS	National Health Service
PID	Primary Immunodeficiency Disease
SNBTS	Scottish National Blood Transfusion Service
UK	United Kingdom
UKPIN	UK Primary Immunodeficiency Network
UoE	University of Edinburgh
vCJD	variant CJD

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SUMMARY

Variant Creutzfeldt-Jakob Disease (vCJD) is a very rare disease, associated with an abnormal form of a naturally occurring protein (the prion protein), the presence of which can be detected in certain body tissues. To date, a total of 177 cases have been reported in the UK, most of which have been attributed to eating bovine spongiform encephalopathy (BSE) contaminated meat. However infection may be spread through blood transfusion or treatment with certain plasma products. Donated plasma is used to make a range of blood products, including immunoglobulin, which has a variety of uses including as a life−long treatment in patients with a group of diseases known as primary immunodeficiency diseases (PID). In the UK, two intravenous immunoglobulin products were available for treatment between 1996 and 2000. The products were made from plasma from UK donors. For PID patients treated with these products there is a low but additional (to the background risk through eating meat) risk of their being infected with vCJD. By following-up these patients over several years, and testing any available tissue (for example, the tissue left over from routine biopsies) and blood (when a suitable blood test becomes available) for the abnormal prion protein that causes prion disease, this study can look for evidence of vCJD in patients with PID, assess if the infection was acquired through the use of these products and consider the wider implications to patients' and public health.

1. INTRODUCTION

Variant Creutzfeldt-Jakob Disease (vCJD) is a very rare neurodegenerative disease and one of a group of diseases called prion diseases, all of which are associated with an abnormal form of a naturally occurring protein (the prion protein), the presence of which can be detected in certain body tissues.

The first case of vCJD was reported in the United Kingdom (UK) in 1996. To date, a total of 177 cases have subsequently been reported, the last occurring in 2012 [NCJDRSU, 2014]; all those tested have been methionine homozygous at codon-129 of the prion protein gene. However, the prevalence of detectable abnormal prion protein in the general population, indicating vCJD carrier status in the absence of disease, is estimated at 1 in 2000 people [Gill et al.,2013]. All codon-129 genotypes are susceptible to infection and have been identified amongst the asymptomatic carriers of vCJD.

Most cases of vCJD have been attributed to dietary exposure to bovine spongiform encephalopathy (BSE) contaminated meat [Ward et al.,2006]. However secondary transmission has occurred through blood transfusion [Llewelyn et al.,2004; Peden et al., 2004] or treatment with certain plasma products [Peden et al., 2010]. Transmission may also be possible in the wider medical setting, for instance through organ/tissue transplantation, or certain types of surgery, although no instances of this occurring have been identified to date [Molesworth et al.,2014]. At the time of writing, there is no blood test for prion infection that can reliably tell us if someone is infected with vCJD before they develop symptoms of disease, although scientists are working on this.

2. RATIONALE

To date, there have been four instances of blood-transfusion associated transmission of the vCJD agent. These occurred in patients who received red blood cells from donors who were asymptomatic at the time of donation but who subsequently went on to develop vCJD. In addition there has also been one instance of blood-product associated transmission in a patient with a bleeding disorder. This patient, identified by the UK Haemophilia Centre Doctors Organisation through their enhanced prion surveillance study amongst patients with bleeding disorders, died with no history of neurological disease but had received 400,000 units of UK-sourced plasma products in the course of their treatment to which the transmission was attributed; the products included >9000 units of implicated factor VIII from a single donor who died of vCJD [Peden et al., 2010].

Donated plasma is used to make a range of blood products in addition to factor VIII. These include immunoglobulin, which has a variety of uses including as a life−long treatment in patients with a group of diseases known as primary immunodeficiency diseases (PID). In the UK, two intravenous immunoglobulins were introduced in 1996 and produced until 1998 from plasma donated in the UK up to and including 1997: Vigam (BPL, produced for England & Wales) & Human Immunoglobulin (SNBTS, for Scotland). The products were available for dispensing up to the end of 2000 (when the final stocks had either been used or expired). No donors contributing plasma for the manufacture of Human Immunoglobulin are known to have developed vCJD. However, nine UK donors who subsequently developed vCJD are known to have donated plasma which was included in nine batches of Vigam released between 1996 & 98 (implicated batches).

In September 2004 the Department Of Health asked immunologists to identify patients who had received Vigam between 1996 & 2000 and to make individual risk assessments for exposure to abnormal prion protein , based on the level of infectivity of each Vigam batch (each batch had a different calculated infectivity, depending on the plasma donations that were used) and the total dose received. Patients who had been exposed to $0.02ID_{50}$ or greater (a theoretical 1% risk), would be considered at an additional risk to the general population risk of vCJD from exposure to BSE and asked to take special public health precautions to minimise the risk of further transmission in the healthcare setting [Public Health England, 2013].

No PID patients were assessed as crossing the "at-risk" threshold and so no special precautions were required. However there remains a low but additional risk of their being infected with the vCJD agent through the use, in their treatment, of Vigam and Human Immunoglobulin products between 1996 and 2000. Moreover this risk might be an underestimate if more plasma donors have been or become carriers of infection without showing signs of disease.

3. AIMS & OBJECTIVES

A. AIMS

1. To identify whether there is evidence of abnormal prion protein in the body tissues of primary immunodeficiency patients exposed to UK sourced immunoglobulin between 1996 and 2000.

2. If yes, to assess the likelihood that vCJD infection was acquired through the use of these products in the individuals concerned, and consider the wider implications to public health.

B. OBJECTIVES

1. To test body tissues for evidence of abnormal prion protein / vCJD.

2. To determine how blood tests results (when such a test becomes available) correlate with the results from examining tissues. However no test is available at present that can tell us if someone is infected with CJD before they develop symptoms of the disease.

3. To describe the type of infection, its clinical phenotype and pathological features, and timing of infection relative to exposure, cumulative dose of immunoglobulin and codon 129 genotype.

4. To assess the risk of infection with vCJD through dietary exposure to infected meat, exposure to UK sourced immunoglobulin and other iatrogenic routes.

The research involves the investigation of patients with an uncertain risk of developing vCJD following exposure to blood products, affording a better understanding of disease epidemiology, and potentially characterisation of clinical presentation and strain variability. It is possible that no cases of infection will be detected. While negative findings are important, a positive finding will prompt reconsideration of the risk of secondary transmission through a range of blood products, with implications for public health.

4. GOVERNANCE

This study began in 2006 as a four-year study under the sponsorship of Central Manchester and Manchester Children's University Hospitals NHS Trust, and was subsequently extended to 2015 [Helbert et al, 2015]. In April 2015 study management transferred to the National CJD Research & Surveillance Unit, under the sponsorship of the University of Edinburgh, and continues as an ongoing activity involving the long-term follow-up of participants. The study has received ethical approval by Greater Manchester South National Research Ethics Service Committee (protocol 05/Q1403/98, approved 9th June 2005).

5. METHODS

5.1 STUDY DESIGN, POPULATION & SETTING

This is an epidemiological study involving the recruitment and long-term follow-up of a defined patient group. The study aims to include all specialist immunology centres with eligible PID patients throughout the UK. It is hospital based, involving the collection of blood and screening of tissue samples, including

post-mortem investigations, for evidence of abnormal prion protein / vCJD. Each centre will have a designated site-specific Local Investigator. The study will be coordinated centrally at NCJDRSU by the Chief Investigator and a project-dedicated Research Nurse.

5.2 CASE DEFINITION & ASCERTAINMENT

A. INCLUSION

Patients with PID who received UK sourced immunoglobulin products (BPL Vigam and/ or SNBTS Human Immunoglobulin) between December 1996 and December 2000 are eligible for inclusion in the study, with informed consent.

All PID centres in the UK should keep records of their patients and treatments. When centres are recruited into the study, these records will be examined by the local investigator who will identify any eligible patients. The size of the population of patients with PID who were exposed to UK sourced immunoglobulin between 1996 and 2000 is estimated at about 175.

B. EXCLUSION

Patients will not be considered eligible if there is no documented evidence of exposure to UK sourced immunoglobulin and/or and the underlying diagnosis does not meet European Society for Immunodeficiencies (ESID) diagnostic criteria (http://www.esid.org/).

Adults lacking the capacity to consent will also not be recruited into the study. This may be a source of bias: prion disease is a neurodegenerative condition so there is the very small possibility that a lack of capacity may be linked to infection with the vCJD agent. However, patients with features of dementia will be referred to the appropriate local specialist and, if CJD is suspected, then the patient will be referred to NCJDRSU for further assessment, in line with UK standard prion disease referral procedures (see section 9.2).

C. LOSS OF CAPACITY DURING THE STUDY

Rarely, patients may develop dementia or mental incapacity in the course of the study, because of their immune deficiency. If a participant loses capacity to consent during the study, the study can continue under existing consent arrangements (see section 5.12). This will enable investigations for evidence of abnormal prion protein / vCJD.

5.3 RECRUITMENT OF IMMUNOLOGY CENTRES

The local lead investigator at each immunology centre will be informed of the (changes to) protocol and through them patients will be invited to join / continue to participate in the study.

A. Specialist immunology centres are identified as potential research sites through the UK Primary Immunodeficiency Network (UKPIN) of clinicians and associated UK PID registry. Lead clinicians at each centre should be sent a letter inviting the centre to participate (centre invite letter.doc). This letter asks for confirmation of numbers of patients who received UK sourced immunoglobulin between December 1996 and December 2000, and whether they are children or adults.

B. All centres should be approached. Centres already participating in the study will be informed of any changes of protocol, as well as being asked to check that all eligible patients have been identified. Centres not joining the study, including those refusing to participate and those that have previously shown interest but have been too busy to join, will be approached again and asked to join.

C. All PID centres in the UK should keep records of their patients and treatments. Each centre will have a designated site-specific Local Investigator. When centres are recruited into the study, these records will be examined by the Local investigator who will identify any eligible patients.

For centres indicating that they do wish to participate / continue participating, the Research Nurse can offer to help prepare/amend the applications for IRAS and R&D approval.

D. A record should be kept in the study database (see section 8.2) of which centres have been invited to participate, whether a R&D application has been made and the number of eligible adult and child patients at each centre.

5.4 INITIAL APPROACH TO PATIENTS

Patient contact cannot begin until the relevant centre has R&D approval, and patients have agreed to a meeting with the study Research Nurse.

A. The NCJDRSU Research Nurse will telephone the Local Investigator to check that they are confident with the information they will need to provide patients. If necessary, the Research Nurse can provide face to face support for Local Investigators prior to recruitment.

B. The Research Nurse will ask the Local Investigator to explain the study to eligible patients attending for routine appointments. The clinic staff will then explain the research study to the patient as he/she attends for routine appointments provide an information sheet.

(NB. No younger people (under 16) are currently participating in this study and as time progresses the possibility of new recruits amongst this age group will become less likely: the youngest possible recruit can be born no later than the end of 2000 and will reach 16 years by the end of 2016. In the event that someone under 16 is identified as eligible for inclusion then their parent/guardian will be involved in the recruitment process, and if appropriate can provide consent on their child's behalf).

C. Participants who joined the study previously will be informed there has been an extension to the study with changes to protocol by the Local Investigator at their next routine appointment; the patients will be re-issued with updated information sheets.

For patients for whom English is not the first language, arrangements for a translator / advocate should be made. If the patient requests an information sheet in their own language, this will be prepared by the Research Nurse using an appropriate translator/advocate.

D. Patients will then have an opportunity to reflect on whether they wish to meet the new research nurse and will indicate their assent to the Local Investigator (a SAE and assent form will be provided if necessary) or, alternatively, the local investigator will contact the patient after at least 1 week and ask if they would agree to meet the study research nurse in order to discuss the study in more detail and consider joining/continued participation. The Research Nurse cannot meet or initiate contact with patients at this stage, however all patients will be given the option of contacting the Research Nurse directly if they wish, in order to discuss the study and any questions they may have.

E. If a patient decides they do not wish to take part in the study, the Local Investigator will record this information and let the Research Nurse know. The Research Nurse will record the refusal and if a child or adult in the recruitment table of the study database. No patient identifiers will be recorded.

F. If the patient wishes to meet the Research Nurse and consider joining/continued participation, the Local Investigator will tell the Research Nurse and arrange an appointment.

G. Check that the patient is eligible for inclusion in the study: the patient must have received UK sourced immunoglobulin between December 2006 and December 2000, and the underlying diagnosis should meet ESID diagnostic criteria (http://www.esid.org/).

5.5 RECRUITMENT VISIT & INITIAL ASSESSMENT

Although assent to meet the research nurse has been given beforehand, consent to join/continue participating in the study can only be taken at the recruitment visit. This ensures participants are adequately informed about the project, its relevance and the consent process. Before the interview the patient will have received information about the study and what participation involves (see section 5.4).

A. The recruitment visit is part of a routine outpatient appointment attended by the patient (and any family, friend or advocates), the local investigator and the project Research Nurse. A one hour appointment should be booked, although it is possible the patient will not wish to use all their allocated time. The Local Investigator may disclose the patient's name to the Research Nurse but no further information should be provided until the patient has given informed consent. A translator / advocate should be booked in advance, as required.

B. At the start of the recruitment visit, the Research Nurse will again detail what is involved, namely: the regular donation of blood and/or tissue samples for testing for abnormal prion protein, as well as the inclusion of limited information in a study database relating to the patient's underlying diagnosis, their exposure to blood/blood products, and results of any investigations for evidence of abnormal prion protein / vCJD performed on the patient's tissue.

C. The Research Nurse will allow time for questions from the patient, their relatives or friends. The Research Nurse may need to ask questions to confirm that the patient or relatives understand the study. The Research Nurse and local Investigator will be alert for signs of distress and may, as appropriate, end or pause the appointment.

D. All subjects will then be asked if they wish to join/continue participating, with consent asked separately for the different elements of the study

- ☐ for participation, including registration of patient data and Ig exposure
- ☐ for review of blood/blood products & other risk factors
- ☐ for testing of residual tissue for evidence of vCJD
- ☐ for post-mortem investigations for evidence of vCJD
- ☐ for prion-protein codon-129 polymorphism typing
- ☐ for 2-yearly donation of blood for storage and future testing
- ☐ for annual telephone follow-up, including confirmation of appointments

For consent to be valid, all individuals who agree to participate will be required to sign a Consent Form. All participating patients must give consent for inclusion on the patient database. It is possible to opt out of other elements of the study.

E. Patients declining participation should be thanked for their time. The local investigator should record this information and the Research Nurse will record that there was a refusal and if a child or adult in the recruitment database.

F. If a patient or parent gives consent for the study, they will be given a unique study number, which will be recorded in the patient's notes, and a copy of the consent form to keep. The original will be kept in the patient's notes and copies in the main and local site study files. For patients who decide to take part, permission will also be sought from the patient for an outline of the study to be sent to their GP, for information.

G. For participants who joined the study previously, changes in the study will be discussed, and the patient invited to continue participating. If the patient wishes to continue the Research Nurse will check the patient details are correct, obtain written consent and give them a copy of the consent form to keep. The original will be kept in the patient's notes and copies in the main and local site study files. For patients who decide to take part an outline of the study will also be sent to their GP, for information.

H. At the end of the Recruitment visit, the study research nurse will ask if the patient or their family has any further questions and thank them for their help. A date should be scheduled for the next follow-up appointment, which could be either an annual telephone call or face-to-face meeting (see section 5.11).

I. If an existing participant does not wish to continue in the study ask if this applies to some or all of the study components. If the participant does not want to donate blood or residual tissue check if stored samples to the point of withdrawal and existing consent for post-mortem investigations and patient data can be retained until testing/analysis is completed. If declined, the withdrawal from the study and details of actions required and undertaken, with dates, should be recorded by the local investigator and research nurse in their respective study notes (see section 5.12).

J. Opportunities for post mortem examination and investigations for evidence of prionopathy will be discussed with the patient in life. Although expressed consent will not be needed while the participant is still living, the participant's wishes will be recorded if a decision is made. It will be suggested to the patient that they discuss their wishes with their relatives, so that the relatives are more prepared in the event of the participant's death (see section 5.13).

5.6 PARTICIPATION, INCLUDING REGISTRATION OF PATIENT DETAILS & IG EXPOSURE

A. If the patient gives consent for the study, the Research Nurse will record this information on the consent form, along with the unique study number.

B. The study number, name, date of birth and contact details of the patient, together with the immunology centre and GP contact details, will be recorded on a questionnaire form and in the patient database. Details of recruitment visits, consent status and follow-up appointments will also be recorded to facilitate participant follow-up. The unique study number is assigned for data management purposes, including pseudonymisation and the association of data between relevant data forms.

C. Patient records will also be reviewed in order to document the underlying diagnosis and all immunoglobulin treatment between December 1996 and December 2000. These data will be gathered at the recruitment visit by completing the batch documentation tool component of the questionnaire form.

D. Much of this work will have been done in September 2004, following advice from the Health Protection Agency (now Public Health England). If the data are incomplete, ask the local team to request records from other hospitals where the patient has received treatment. Patients will receive immunoglobulin every two, three or four weeks. Aim to review this data at the recruitment visit and document on an exposure review form, all immunoglobulin infusions between December 1996 and December 2000. Calculate the total dose of each batch. These details will be recorded in the database. For participants who have already joined the study, this information will have already been gathered.

E. For patients participating/continuing in the study, a letter should be sent to their GP providing an outline of the study and updating the GP of any relevant changes, for information.

5.7 REVIEW OF BLOOD TRANSFUSIONS AND SURGERY

A. If the patient consents, at the recruitment visit ask the patient and also check the Ig centre patient medical records for past medical history, including their history of blood transfusion or receipt of other blood components or blood products, any surgical operations, where they have lived and worked and any family history of neurodegenerative disease. Record the answers, including details of the location, dates, amounts and batch/unit numbers received on the exposure review form. This is to ascertain the risk of infection via iatrogenic routes should a risk assessment be undertaken and inform any related public health actions should the need arise. These details should also be recorded in the study database.

B. For participants who have already joined the study, the Research Nurse should check for any recent history of blood transfusion or receipt of other blood components and surgery in the intervening period since the last visit.

C. This is to help generate hypothesis as to risk factors for disease. It may also help identify the most likely route of infection in the event of a positive finding and inform any related public health actions should the need arise.

D. If the patient consents, at the recruitment visit the participant/their relative will be asked questions about the participant's past medical/dental histories, including their donation and receipt of blood/blood products, any surgical procedures and where they have lived and worked and any family history of neurodegenerative disease, the answers to which will be recorded on a questionnaire form. The questionnaire will normally take half an hour.

5.8 PRION PROTEIN CODON-129 GENOTYPING

Codon-129 genotype is a risk factor for developing vCJD at the population level and may help to classify the type of prion infection, but does not indicate a specific genetic risk for CJD at the individual level. Genetic sequencing is outside the remit of this study and will not be performed.

A. The codon-129 typing is a one-off investigation performed following the recruitment visit. On the day of the recruitment visit, the Research Nurse should check whether the patient is having routine blood samples taken on the day of the recruitment visit and make sure that any study blood samples consented for are taken. If this is not happening on the day of the recruitment visit, the Research Nurse should make sure that the local Immunology team know which samples to collect and how to store them.

B. If the patient consents, ensure that a 2 ml EDTA sample is taken, labelled and transported back to NCJDRSU for registration, processing and testing (see section 6). NCJDRSU will arrange for the disposal of any residual blood and genetic material remaining after the end of the study. The codon-129 polymorphism result should be recorded in the study database.

5.9 DONATION & STORAGE OF BLOOD FOR FUTURE TESTING

If the patient consents to this part of the study, blood will be taken every 2 years from the recruitment date for storage and future testing.

A. On the day of the recruitment and subsequent visits, the Research Nurse should check whether the patient is having routine blood samples taken on the day of the recruitment / follow-up visit and make sure that any study blood samples consented for are taken. If this is not happening on the day of the recruitment visit, the Research Nurse should make sure that the local Immunology team know which samples to collect and what to do with them.

B. If consent has been given for storage and future testing, ensure that one 10ml EDTA sample and one 5ml citrate sample are taken, labelled and transported to the CJD Resource Centre at the National Institute for Biological Standards and Control (NIBSC) for registration, processing, storage and future testing (see section 6). Record the date the samples have been taken in the study database.

5.10 TISSUE IDENTIFICATION, COLLECTION & TESTING

Existing tissue samples will be obtained from lymph node, tonsil, spleen, gut (includes the appendix), and bone marrow trephine. The numbers of samples available for the research will vary with the number of individuals recruited, however about 5-10 patient referrals (each including one or more samples) may be made to NCJDRSU each year.

A. On the day of the recruitment and subsequent visits, the Research Nurse should ask the patient and also search the hospital notes for evidence of past operations or biopsies as part of their routine care. The 'history', 'correspondence' and the 'results' sections of the notes should be reviewed, making a note of any biopsies, their anatomical site, date and any laboratory number associated with the biopsy. If the patient has been treated at another hospital, ask the local team to make the other hospitals notes available for review.

B. If tissue samples were taken, the Research Nurse should contact the Consultant Histopathologist or Senior Chief Biomedical Scientist in Histopathology requesting the sample (s) (pathologist letter). In many cases, these individuals may be known to the local immunologist and it may be appropriate for them to make initial contact.

C. Formalin fixed paraffin embedded tissue blocks and frozen tissue are appropriate for testing. The research nurse should liaise with the local histopathology team, answer any queries and organise for them to send samples to the NCJDRSU in Edinburgh for testing. Once received at NCJDRSU, the samples will be registered for processing and investigated for evidence of abnormal prion protein/vCJD (see section 6).

D. After samples have been tested in Edinburgh the remaining material will be returned to the source hospital where it may be required for further routine diagnostic testing. The sample details, including results of any investigations undertaken on the samples, should be recorded in the study database.

5.11 ANNUAL FOLLOW-UP

A. If consent has been given for the regular donation of blood for storage and future testing, then the research nurse should arrange a follow-up appointment with the patient and the local investigator at the recruitment meeting. This would normally be in 2-years' time at the hospital as part of a routine appointment. This can be a tentative arrangement, to be confirmed in consultation with the local investigator closer to the time. If the patient agrees explain that the research nurse may also call them directly in advance of the meeting to confirm the appointment.

B. If the patient agrees to annual follow-up by telephone, then contact details should be recorded and a date for the call scheduled. Again, this can be a tentative arrangement, to be confirmed in consultation with the local investigator closer to the time.

C. One month before either type of follow up appointment, the Research Nurse will contact the local Immunology team to confirm arrangements and check the patient contact details are up-to-date and ask them to remind the patient(s). The purpose of the follow-up is to provide the patient with any new study related information and an opportunity to ask questions. The research nurse will also check with the patient if he/she has had any operations, received any blood/blood products

or had any changes to their ongoing Ig treatment, as part of the ongoing review of blood transfusions and surgery.

D. Before the follow-up meeting the Research Nurse should consider if there is new information that patients may need to receive. This may come from publications, meetings, or the study itself, and should be discussed, in addition, between the NCJDRSU study team and local investigators. If the patient has agreed, then the research nurse may also call directly to the patient to confirm the appointment.

E. "Meet" the patient and give them any new information and an opportunity to ask any questions. Ask whether they wish to continue to participate and check their details are correct. A note should be made of the meeting and kept on file.

F. Ask the patient if, in the past year, they have had any operations, received any blood/blood products or had any changes to their ongoing Ig treatment.

G. The research nurse should also check with the local team whether any biopsies/operations have occurred in the last year. Similarly check for recent history of blood transfusion or receipt of other blood components, and change to treatment. Review the medical notes to obtain necessary details, request and arrange transport for testing as described in section 6.

H. If biennial blood sampling is due, ensure that blood samples are taken (see section 6).

I. At the end of the appointment, ask if the patient or their family has any further questions and thank them for their help. Schedule a date for the next annual telephone call and biennial follow-up appointment.

5.12 OPT OUT / WITHDRAWAL

A. Once a patient has consented to participate it is assumed the patient agrees to remain in the study until such a point as they opt out or are withdrawn.

B. Patients will be asked annually if they wish to continue with the study, however consent to participate in all or part of the study can be withdrawn by the patient at any time, without compromising their care.

C. If an existing participant does not wish to continue in the study ask if this applies to some or all of the study components and identify which ones. If the participant does not want to donate blood or residual tissue check if existing stored samples and patient data already held can be retained until testing/analysis is completed, and if their wishes for post-mortem investigations still hold. Check if they would still like annual follow-up by telephone. Obtain written agreement from the patient if any of these apply.

D. If the participant loses capacity to consent during the study, new blood and tissue samples may still be collected under existing consent arrangements. In these situations check with the patient's representative they are happy with these arrangements and if they would like annual follow-up by telephone on the patient's behalf. Obtain written agreement from the patient's representative using the Consultee declaration form. Consent will be retaken when capacity is regained.

E. It will be possible to withdraw tissue up until the time it is tested and NCJDRSU will arrange for the respectful disposal of any remaining tissue in line with standard practice. Data can be withdrawn on request by deletion from the study database.

F. The withdrawal from the study and details of actions required and undertaken, with dates, should be recorded by the local investigator and research nurse in their respective study notes

5.13AFTER DEATH

A. A post mortem will provide definitive confirmation of prion disease and can be informative as to other diagnoses, so an examination may be undertaken for both research and diagnostic purposes.

B. The research nurse will discuss the possibility of post-mortem investigations for evidence of prionopathy with the patient, if not at the initial meeting at an appropriate time in the follow-up process. Patients will be asked if they agree to a post-mortem examination and investigation fpr evidence of abnormal prion protein/vCJD. The patient's wishes will be recorded if a decision is made, but expressed authorisation will not be needed until after death - at which point the relative will be given a hospital post-mortem authorisation form, which they will be asked to consider and complete.

C. The patient will be asked to discuss their wishes with their relatives.

D. In the event of a patient's death, the families will be asked to contact the local team (who in turn should inform the Research Nurse), or if they wish the family may choose to contact the research nurse directly. The families and local team will have been given a phone number to call as soon as possible after the death has occurred, so that post-mortem examination can be arranged.

E. When patients give in-life consent for post-mortem examination, the Research Nurse will have arranged for the Chief Investigator to write to the local Pathologist, giving an outline of the study and requirements from them in case of the patient's death including a protocol for autopsy (enclosed – Pathologist Letter). Local pathologists are invited to contact the Lead Investigator to discuss any potential problems with doing post-mortem examinations, in advance.

F. Establish whether a Coroner's/Fiscal post mortem will be required (for example because of accidental or unexplained death). If so, it is still possible to collect samples, but the local Coroner's/Fiscal office should be informed if the patient has given consent for the research study, and provided with details of research ethics committee approval. If a Coroner's/Fiscal post-mortem examination is required, the patient's relatives cannot prevent this from happening.

G. If a Coroner's post-mortem examination is not required, it is very likely that the local team will wish to speak to the patient's relatives soon after death. This is an opportunity for the local team to raise the issue of post-mortem: if the patient gave consent then it is likely that the patient's relatives will be aware of this, will not object, and arrangements can go ahead.

   If the patient did not leave any formal authorisation then this must be sought from the representative/relatives using the standard hospital post-mortem consent form. The local team will carry out most of the liaison with the relatives and pathologists, however the Research Nurse and Laboratory Manager (NCJDRSU) will make themselves available for offering telephone advice during this period.

H. Consent will be requested for a full post-mortem . Normally the post mortem will be conducted in a local hospital by a pathologist between one and four days after death, and every effort should be made to avoid delay to the funeral arrangements. After this the body will be returned to the undertakers.

I. Transport to and from the mortuary will normally be undertaken by the family's chosen funeral director. There should be no cost passed on to the family with regard to the transport of the body.

J. The tissue samples will be collected from brain, tonsil, lymph node, appendix and spleen and will then be investigated by NCJDRSU for evidence of CJD, including standard histopathology, immunohistochemical and biochemical investigations. It will be possible to withdraw post-mortem consent and tissue analysis up until the time the tissue is tested; in this event we will arrange for the respectful disposal of any remaining tissue.

K. It is possible that relatives will object to post-mortem examination after being reminded that the patient had given consent. In this situation, there is a conflict between the wishes of the deceased patient and their relatives. The investigation team may wish to respect the wishes of relatives in view of the distress this may cause.

L. The cause of death and results of any post-mortem investigations should be recorded on the study database.

6. SPECIMEN TRANSPORT, PROCESSING & TESTING

Appropriate safety precautions will be employed by all personnel in the handling of specimens from the time of tissue sampling, in accordance with health & safety policy.

6.1 BLOOD FOR CODON-129 GENOTYPING.

A. A 2ml EDTA sample should be taken, labelled with the patient's study number , date of birth and date of collection only and the sample transported at ambient temperature back to NCJDRSU for registration in the laboratory the following working day. Samples will then be stored in a -80C freezer at NCJDRSU prior to testing.

B. Friday collections may be kept refrigerated over the weekend before registration at NCJDRSU on Monday morning. Occasionally, if a large number of samples are to be collected then they may be frozen locally and stored safely until ready for transport. NCJDRSU can advise on the transport of these and other frozen material.

C. Genetic material (DNA) will be extracted from the blood samples and molecular codon-129 subtyping will be undertaken by NCJDRSU. Genetic sequencing is outside the remit of this study and will not be performed. The codon-129 polymorphism result should be recorded in the study database.

D. Residual blood and genetic material remaining after testing will be retained by NCJDRSU as part of the investigation record for up to 5 years after completion of the study and then disposed of if of no further value to this research project.

6.2 BLOOD FOR STORAGE & FUTURE TESTING

A. One 10ml EDTA and one 5ml citrate blood samples will be collected every two years. These should be labelled with the patient's study number, year of birth and sample collection date only. The samples should then be posted the same day to the CJD Resource Centre at NIBSC, using approved secure packaging for posting biological substances at ambient temperatures (blood) and accompanied by a study sample form. Record the sample details in the study database.

B. Friday collections may be kept refrigerated over the weekend before posting to NIBSC on Monday morning.

C. On receipt at NIBSC the EDTA and citrate samples will be registered. Some whole blood will then be retained from each sample, the rest will be separated into buffy coat, plasma and red

blood cell components according to the NIBSC testing standards. The samples will then be stored at -80C for future testing.

D. The staff at NIBSC will not be told the participant's identity, and an oversight committee will determine the specific conditions of the use of the samples before approving their release for such testing. Test results will be fed-back to the Research Nurse at NCJDRSU and recorded on the study database.

E. Samples existing from the Manchester study will be transferred to NIBSC for long-term storage, in accordance with national Health & Safety Regulations.

F. Blood samples will remain at the CJD Resource Centre at NIBSC, where they will be stored indefinitely and used anonymously for prion testing; they will then be disposed of lawfully when they have served this purpose.

6.3 TISSUE SAMPLES

A. Tissue samples from biopsies or past operations will be obtained from lymph node, tonsil, spleen, gut (includes the appendix) and bone marrow trephine.

B. Formalin fixed paraffin embedded tissue blocks and frozen tissue are appropriate for testing, and may be stored at the hospital until ready for sending. The tissue samples should be anonymised before leaving the source hospital and being sent to NCJDRSU. A study tissue form should accompany the samples, containing the source laboratory identification number, patients' study number, date of birth and sample collection date.

C. The local team may wish to make a record so that once investigations are complete the sample can be returned to the source hospital and its original place of storage.

D. The research nurse should notify the NCJDRSU laboratory of retrospective samples being sent.

E. Samples will usually be available as tissue blocks; no specific precautions are necessary for sending blocks by post however they should be packaged appropriately to prevent damage to the samples in transit.

F. If frozen tissue is available, this may be stored in a -80C freezer until ready for collection and transported in dry ice. The frozen material should be held in the local laboratory until ready to be transported to Edinburgh, in accordance with national Health and Safety regulations. NCJDRSU can advise on the transport of these and other frozen material.

G. Once received at NCJDRSU, the samples will be registered for processing and investigated for evidence of abnormal prion protein/vCJD. Tissue samples will be processed for a range of histopathological and biochemical investigations. These include standard haematoxylin & eosin staining, immunocytochemistry and PET blotting to identify evidence of abnormal prion protein / pathological change (fixed tissue) and standard diagnostic Western blot and high sensitivity sodium phosphotungstic acid (NaPTA) precipitation for abnormal prion protein (frozen tissue, most likely available through autopsy). Analysis of frozen material is more sensitive for the detection of prions. Genetic sequencing is outside the remit of this study and will not be performed.

E. The sample details, and outcome of these investigations, including evidence of vCJD, sCJD or other prion-associated pathology should be recorded in the samples database.

F. Slides cut from the blocks and used for investigations will be retained by NCJDRSU as part of the investigation record for up to 5 years after completion of the study. They will then be disposed of, if of no further value to this research project study. Tissue blocks will be returned to the source hospital once testing has been completed where they may be required for further routine diagnostic testing. However, if any samples show evidence of prion infection, tissue blocks will normally be retained with the slides at NCJDRSU pending the 5-year review.

6.4 AUTOPSY SAMPLES

A. Fixed and frozen brain tissue samples from frontal lobe and cerebellum; fixed and frozen tissue samples from tonsil, lymph node, appendix and spleen. A protocol is available for specimens to be retained at autopsy for the screening of abnormal prion protein. The CJD surveillance team will be happy to advise on/arrange collection of specimens.

B. Autopsy tissues remaining after samples have been taken will be handled according to the wishes of the relative (for retention for other research purposes, disposal via the source hospital, or return for cremation and burial).

C. Any autopsy tissues of diagnostic value (ie showing evidence of CJD or other prionopathy) routinely retained at NCJDRSU as part of the medical record.

D. Tissue slides will be retained by NCJDRSU as part of the investigation record for up to 5 years after completion of the study. They will then be disposed of, if of no further value to this research project study.

7. ANALYSIS

7.1 PRIMARY OUTCOME

A. Evidence of abnormal prion protein in the body tissues of primary immunodeficiency patients exposed to UK sourced immunoglobulin between 1996 and 2000, including a description of the type of infection, the clinical and pathological features, and timing of infection relative to that of exposure and any effects of the dose of immunoglobulin received.

7.2 SECONDARY OUTCOME

A. Assessment of the likelihood that prion infection was acquired through the use of these products, and consideration of the wider implications to public health.

B. Assessment of the relationship between blood tests results (when a blood test becomes available) and results from examining tissues.

7.3 METHODS OF ANALYSIS

A. Progress in the study will be continually assessed against the study objectives namely:

1. To identify whether there is evidence of abnormal prion protein/vCJD in the study population; to describe this evidence in terms of blood and other body tissues investigated;

2. If yes, to describe positive findings in relation to the type of infection, and the clinical, pathological and epidemiological characteristics of the patients involved;

3. To describe the timing of infection relative to exposure and any effects of the cumulative dose of immunoglobulin received and codon 129 genotype.

4. To assess the risk of infection with vCJD through dietary exposure to infected meat, exposure to blood/blood products and other iatrogenic routes, and thereby the likelihood that vCJD infection was acquired through the use of UK sourced immunoglobulin

B. Regular analyses will include progress in recruitment and investigations, a summary of research findings and assessment of the implications to patients, epidemiological understanding and public health. Positive findings will be published as case reports and/or syntheses of research findings, as appropriate.

C. Missing data will be retained as such as this is appropriate to answering the research question and statistical analyses involved. If patients withdraw then the information they contribute to study up to the point they withdraw will be retained unless they request this is deleted. Data and tissue can be withdrawn on request, leaving the minimum record required for audit purposes and where relevant to the medical record. The withdrawal from the study and details of actions required and undertaken, with dates, should be recorded by the local investigator and research nurse in their respective study notes.

D. The study results will be shared with local and national stakeholders, in particular, both clinician (UKPIN) and patient networks.

7.4 INTERPRETATION

A. If 1 in 2000 people are infected with vCJD in the UK general population then in a study population of 200 patients we might expect 0.1 patients to show signs of infection. If the additional risk in PID patients of developing vCJD is below 1%, then depending how close to this threshold each patient is, we might expect up to 2 cases in the study population.

B. In the event of a positive finding, the Chief Investigator will confirm the level of certainty in the result. She will then consult with public health authorities to assess the risk of infection with vCJD through dietary exposure to infected meat, exposure to blood/blood products and other iatrogenic routes, and thereby the likelihood that vCJD infection was acquired through the use of UK sourced immunoglobulin and the wider implications to public health (see section 9 below).

8. DATA MANAGEMENT

8.1 DATA HANDLING

Study data will be held in electronic and paper format. Source data will be checked and validated before electronic data-entry and verification. Papers records will be filed securely at NCJDRSU. Electronic data will be held in a study database with sub-tables, details of which are described below.

8.2 INFORMATION COLLECTED

The totality of information for the research will be recorded as follows:

A. Consent form: Patients who have given consent to participate will have their name recorded on the consent form, alongside the unique study number.

B. Recruitment details: For each specialist immunology centre information will be collected on the numbers of patients with primary immunodeficiency who were exposed to UK sourced immunoglobulin between December 1996 and December 2000, by adult/child status, and numbers who have refused/agreed to participate in the study and whether this decision was

made at the centre/individual level. Also included will be the date the centre was invited, progress/outcome and the local lead investigator contact details. This information will be recorded in a recruitment database, to enable tracking which centres are participating in the study, the stage in the recruitment process and local contact details for centre follow-up. Confidential patient identifying information will not be recorded.

C. Participant details (information about the participant and consent status, exposure details and information regarding the donation, storage, testing and analysis of blood and tissue samples). Other administrative information and adverse events should also be recorded:

i. Patients who have given consent to participate will have their consent status, unique study number, name, contact details, date of birth, gender, underlying diagnosis, dated ADL (alive/dead/left the study) status and cause of death recorded on a questionnaire form and entered into an electronic database, alongside the immunology centre and GP contact details and details of recruitment visits and follow-up appointments. Patients identifiers will be held separately from other study data; patient records will be identified by use of the unique study number.

ii. Data on exposure to batches of immunoglobulin should be gathered by completing the patient review form. This should include all immunoglobulin infusions between 1996 and 2000. In addition, if the patient has a history of blood transfusion or has received other blood components, and surgical operations record details similarly. For each batch/unit, the batch/unit numbers, start and end dates and total dose received, location should be recorded in an exposure database, alongside the patient's unique study number. Patients will be identified in this table by use of their unique study number.

iii. Samples: At the NCJDRSU samples will be brought to the laboratory reception area as they are received for computer-registration of the sample details. They will be flagged as belonging to the PID study and assigned a unique donor number to enable tracking within the Unit of all specimens associated with that tissue referral. The unique PID study number will be retained as it allows the linking of specimens to the same individual. The specimens will then be stored according to standard procedures, ready for processing. At NIBSC a similar system of identifying and locating specimens is in place. For any blood and tissue samples taken in life and/or post-mortem, the sample details, including results of any investigations undertaken on the samples, should be recorded in the study database. This should include the sample type (eg. blood/tissue), sampling date (from patient), date sent/received in Edinburgh/NIBSC, alongside the patient's unique study number, and Edinburgh/NIBSC number. Patients will be identified in this table by use of their unique study number.

The participant summary form will be held securely with source data at NCJDRSU in the patient file. Electronic records will be pseudonymised by unique study number.

8.3 DATA PROTECTION AND CONFIDENTIALITY

All NCJDRSU staff have a duty to maintain patient confidentiality. The UoE has records management and information security policies, procedures and guidance on the handling of confidential information. In addition, a NCJDRSU Data Protection and Security Code of Practice provides guidance to staff on the handling of personal identifiable information, to safeguard confidentiality and help ensure data protection and security requirements are being met.

The processing of personal information for this study is registered with the Office of the Information Commissioner as part of the University of Edinburgh (http://www.ico.org.uk, ref Z6426984).

8.4 INFORMATION SECURITY ASSURANCE

All the information collected during the course of the research will be kept confidential. For study purposes, all electronic information is held securely in a cloud-based healthcare trusted research environment, provided by AIMES management services in Liverpool (UK); all paper records are locked in secure cabinets; access to personal information is restricted to authorised personnel (Chief Investigator, Research Nurse and those with IT responsibilities) and at no point in time will personal information be disclosed to anybody outside the investigation team; linkage of records for study analyses, and for follow-up is restricted to authorised personnel and by use of the unique study number. Backups are made in line with University of Edinburgh protocol, no other copies of the database will be made. Where clinical review/patient follow-up is undertaken it will be done by the Research Nurse and as far as possible by the same local clinician.

Procedures are in place to ensure the secure transfer of personal information. Email is NOT considered secure and emailing of personal identifiable information via the internet or transfer by via any electronic media (eg. memory stick) is not permitted, including emails between NHS and University accounts, unless it is encrypted. This information should be communicated early on to local investigation teams.

9. ACTION IN CASE OF POSITIVE FINDINGS

9.1 ACTION IN CASE OF POSITIVE FINDINGS

In the event of positive tests for abnormal prion protein during the study, the following steps will be taken:

A. Chief Investigator will speak to the person responsible for the tests and confirm the level of certainty. All efforts will be made to check that the positive result is not attributable to a laboratory or sample error.

B. The Chief Investigator will notify the following bodies in order for them to re-evaluate the risk assessments for blood products, seek advice on incident management and mitigate any ongoing risk:

    1. The Department of Health (London) and Scottish Government Health Department
    2. The CJD sections at Public Health England & Health Protection Scotland
    3. The Advisory Committee for Dangerous Pathogens TSE Subgroup
    4. The Medical Directors for the National Blood Services

    This notification will be anonymous: relevant patient demographic, clinical and exposure information will be disclosed if relevant for risk assessment purposes, however personal identifiers, including name and geographic location will not be disclosed. The aim will be to ensure that revised information is available within three months of a positive finding.

C. The Chief Investigator will notify the patient support groups and UKPIN (clinician) groups to discuss how to inform patients of the finding, its implications for patients and for any public health actions that should be taken. In deciding they will also take advice from the authorities mentioned above, and should note that the study is conducted on the participants' understanding that they would not be informed of their individual test results. Consequently this may, for example, involve a general communication to PID patients, rather than targeting specific individuals. The Chief Investigator will notify and clear with the study REC the nature of the information prior to the disclosure.

D. It is likely that the information will be first disseminated to Immunology teams (via UKPIN) and from there to individual patients. The Research Nurse will also disseminate information to study patients during their annual reviews. The aim would be that the information is available within

three months of a positive finding, and simultaneously to all Immunology Centres and the patient support groups, in order that patients seeking help are given consistent and timely information.

E. If treatment for asymptomatic prion infection becomes proven or recommended, any action taken to identify candidates for treatment will be discussed with the research ethics committee.

9.2 REFERRAL OF SUSPECT CASES OF PRION DISEASE

A. If there is clinical evidence of prion disease in life and/or pathological evidence after death, then the patient would be referred to the NCJDRSU surveillance team as a suspect case, and further investigations would be undertaken according to standard surveillance procedures.

B. Based on a review of the clinical-pathological information available, a diagnostic report would be submitted to a senior clinician/pathologist. The family would then be contacted with consent of the local clinicians involved, in order to complete the clinical and epidemiological review, and provide information and support where necessary

C. The case will be referred to the local public health team who will follow national guidance on public health action to be taken. If necessary advice will be taken from relevant expert panels (ACDP) as to the handling of unusual presentation or novel forms of prion disease.

10. STUDY MANAGEMENT

10.1 KEY STAFFING

A. Chief Investigator
B. Lead neurologist NCJDRSU (co-applicant)
C. Lead neuropathologist NCJDRSU (co-applicant)
D. Lead biochemist NCJDRSU (co-applicant)
E. Lead scientist NIBSC
F. Research nurse
G. Laboratory manager (NCJDSRU)

10.2MANAGEMENT & OVERSIGHT

A. Oversight of the study is provided by a Steering Group, comprised of a clinical representative (UKPIN), patient representative and public health/blood services representative (SNBTS). The Steering Group will provide intellectual input, practical advice and support to the Study Team. They will meet with a working group of the study team 1-2 times a year and when needed to review progress and discuss publications and any issues arising.

B. There will be an Edinburgh-based study management team, who will meet monthly at the start of the project and thereafter every 3-6 months to evaluate progress and ensure the smooth running of the project. The core team will include the study Chief Investigator and co-applicants, NCJDRSU Research Nurse, laboratory manager and database manager, with additional involvement of other Edinburgh-based laboratory and statistical support staff, the NIBSC project leader and the UKPID registry coordinator as required.

C. The Chief Investigator takes overall responsibility for the conduct of this study and coordination of investigators at different sites. Management of field operations and data management procedures will be by the Research Nurse. Clinical issues will be managed by the study senior clinician. Laboratory procedures will be overseen by the study lead protein biochemist and pathologist.

D. At each immunology centre there will be an on-site lead investigator who is responsible for the conduct of the study at the local site. He/she will ensure the smooth running of the project locally and safety and wellbeing of participants.

10.3OUTPUT AND FEEDBACK

A. The lack of an available treatment for prion disease, or a reliable prognosis associated with a positive result mean that this study is conducted on the participants' understanding that they would not be informed of their individual test results. This has been agreed with clinical and patient networks, with REC approval.

   Note: Under the Data Protection Act (1998) there are provisions for the release of information held about patients if this is requested; participants may therefore have the option of knowing their results if they wish.

B. The study results will be also be shared with local and national stakeholders. In particular, the Lead Investigator and Research Nurse will liaise closely with both clinician (UKPIN) and patient networks, in implementing, developing and providing feedback from the study. The steering committee will also produce an annual information sheet for participants, containing thanks, and update on recruitment and lay information on knowledge of prion biology. Immunology teams will be given information at the UKPIN annual meeting.

C. Progress in the study will be continually assessed against the study objectives namely:

   1.To identify whether there is evidence of abnormal prion protein/vCJD in the study population; to describe this evidence in terms of blood and other body tissues investigated.

   2. If yes, to describe positive findings in relation to the type of infection, and the clinical, pathological and epidemiological characteristics of the patients involved (and how these may differ from other cases)

   3. To describe the timing of infection relative to exposure and any effects of the cumulative dose of immunoglobulin received and codon 129 genotype.

   4. To assess the risk of infection with vCJD through dietary exposure to infected meat, exposure to blood/blood products and other iatrogenic routes, and thereby the likelihood that vCJD infection was acquired through the use of UK sourced immunoglobulin

   Results will be presented to the Department of Health and Scottish Government Health Department, national public health agencies (Health Protection Scotland and Public Health England) and ACDP. The content of these reports will vary but will include progress in recruitment and investigations, a summary of research findings and assessment of the implications to patients, epidemiological understanding and public health.

D. Research findings will be presented at national and international conferences and for publication as reports and as peer reviewed articles in medical journals. Positive findings will be published as case reports and/or syntheses of research findings, as appropriate.

E. Progress reports will be submitted to NIHR/funding body as required.

F. While these reports are likely to contain a descriptive analysis of the data they will not contain patient identifiable information.

10.4ADVERSE EVENTS, BREACHES, DEVIATIONS & VIOLATIONS

All investigators and their team members will comply with the sponsors' (UoE and NHS Lothian) standard requirements on serious breaches of GCP (SOP reference CR003) and on identifying and reporting adverse events (SOP reference CR006) and on deviations and violations (SOP reference CR010), available at http://www.accord.ed.ac.uk/standardopprocs/CRSOPs.html. This study is a non-CTIMP.

Participants will be asked about any untoward medical occurrence by the research nurse at each visit during the study, using open-ended and non-leading questions. Adverse events should be recorded in the site file and assessed for seriousness, causality, severity and expectedness by the PI. Serious adverse events will be reported to the Sponsors, with the exception of those arising as a direct consequence of the participant's immunodeficiency (including for example nervous system infections, malignancies or more rarely dementia and mental illness) and death. Please note, however, that deaths should still be reported to the Chief Investigator's research team, with the study research nurse informed of this as soon as possible after the event occurs (see protocol section 5.13).

11 END OF STUDY

This study is an ongoing initiative involving the long-term follow-up of participants until testing and analysis of tissue samples for the final participant has been completed. Data and tissue will be retained for 5 years past completion of the last date of testing of blood and tissue samples for the final participant, then their storage reviewed. They will be retained if considered of value to the research project, archived if considered to be of future research use, or otherwise permanently deleted/lawfully disposed of.

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13 APPENDIX

A. INSTRUMENTS

1) Protocol
2) Patient Information Sheet & Reply Slip
3) Patient Consent Form
4) Consultee Information & Declaration Form
5) Exposure review form (including Batch Documentation Tool)
6) Letter to GP