CONFIDENTIAL – DRAFT Phonecon

MSBT 10/4

MSBT 10th Meeting 18 November 1996

CJD
From MSBT 9/4 minute 5

Final draft of the proposed retrospective study to examine a possible link between Creutzfeldt Jacob Disease and Blood Transfusion. An application for ethical approval has now been submitted in the required format by Dr R G Will to the Lothian Research Ethics Committee.

Action Required

For information.

FINAL DRAFT - REFERENCES TO BE ADDED

A retrospective study to examine a possible link between Creutzfeldt Jakob Disease and Blood Transfusion

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Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neuro-degenerative disease of humans. The classic clinical presentation consists of progressive dementia, myoclonic involuntary movements and a variety of focal neurological signs. Diagnosis is based on the clinical presentation combined with electroencephalogram and confirmed by pathology, if available. Survival with CJD is short, averaging less than one year and most often between two and six months. There is no known prophylaxis or treatment for CJD, and the disease is fatal in 100% of cases after the onset of clinical signs and symptoms. There is no available screening assay suitable for asymptomatic general populations.

Background

International Epidemiology of Creutzfeldt-Jakob Disease

CJD occurs at a world-wide rate of between 0.5 and 1 case per million population per annum. There is an even distribution by sex. The peak age of onset is between 60 and 65 years of age. Cases in persons under 30 years of age are rare. There are known to be three main forms of Creutzfeldt-Jakob disease: sporadic, iatrogenic and familial. Most CJD occurs sporadically; approximately 10% of CJD occurs with families; the remainder is iatrogenic (less than 1%). An unknown agent is thought to be the cause of a number of brain diseases of animals and man called "Transmissible Spongiform Encephalopathies" (TSE). Bovine spongiform encephalopathy (BSE) is an example of an non-human TSE. While scientific discussions continue to consider the hypothesis that TSE are caused by a virus, it is widely believed that prions (proteinaceous infectious particle) are responsible. Iatrogenic forms of CJD are believed to be caused by case-to case transmission of prions. While some countries have higher rates of CJD, at this time there is no evidence that this is due to transmissible forms of CJD - rather, the higher rates are due to surveillance biases following intensified

surveillance for CJD among clusters in which very high proportions of the cases are familial. Cases have been found in every country in which they have been sought. The following sections review each of the transmission modalities more closely.

Familial CJD

The familial form of CJD is the cause of about ten percent of reported cases and the study of pedigrees suggests an autosomal dominant pattern of inheritance. All familial cases of CJD so far identified have been associated with one of a number of mutations of the prion protein gene.

Sporadic CJD

The sporadic form of CJD, which accounts for the vast majority of CJD occurrences, has an unknown aetiology. It occurs in the population at a rate between 0.5 and 1 per million per year.

Iatrogenic CJD

Fewer than 1% of CJD reports can be attributed to direct transmission between persons with and without CJD. There are three basic circumstances in which CJD has been transmitted between people: instrumentation, tissue transfer and tissue extract transfer. These circumstances are distinguished from transfusion in that all iatrogenic cases identified so far have involved cross contamination with high CNS titres of infectivity either by peripheral or central routes. Where CJD exposure was central (i.e. direct application of CJD to the brain), the incubation periods were quite short, ranging from 16 months (stereotactic EEG) to 45 months (dura mater implant). However, when the route of exposure was peripheral, as with hGH exposure, the incubation period was greatly extended. No cases were reported less than five years after exposure, and the mean incubation period was 13 years. The longest incubation period was 25 years. It

would be reasonable to anticipate that if a highly concentrated source of the infective agent delivered peripherally has a very long incubation period (as occurred with hGH), then a low concentration source of infective agent (as might occur with blood) delivered peripherally (as during transfusion) would also have an extended incubation period.

Creutzfeldt Jakob Disease and Blood Transfusion

1. *Experimental Animal Data*

Infectivity in blood or blood components has been found in both experimental models of CJD and in sporadic cases. These experiments have involved the intracerebral inoculation of blood or blood components and there is only one experiment demonstrating infectivity in the mouse model of CJD by IP inoculation. Whole blood from sporadic CJD has been inoculated intravenously into chimpanzees and this did not result in the transmission of CJD.

2. *Transmission by Blood Transfusion*

In brief, CJD has not been shown to be transmitted by transfusion of blood or plasma products in humans. Studies have attempted to find evidence whether CJD is transmitted by this means, but none has been found. There is not a single reported case of a person who has been proven to have been infected with CJD through blood transfusion or blood-derived products. The description of 4 cases of transfusion related CJD in Australia has not been substantiated and no conclusion can be drawn on the basis of the case report from France involving potentially contaminated albumin infusion, not least because of the very short potential incubation period.

The incidence of CJD is not elevated in patients who have received transfused blood or in the haemophiliac population.

Two studies involving small populations of transfusion recipients have been published. In one, no association between exposure to blood from a person with CJD and subsequent development of CJD was found; in the other development of CJD was not found to be associated with the receipt of blood. Both studies involved relatively small numbers.

International policies regarding blood or blood products from a person with CJD

In the US, the policy of the FDA (memoranda to Registered Blood and Plasma Establishments, August 8th, 1995) is to withdraw and quarantine all blood donated by persons known to have CJD, donors receiving pituitary-derived human growth hormone injections, donors who are blood relatives of a person with known CJD and donors receiving dura mater transplants. Persons receiving the blood of a person known to have CJD are not being informed as a matter of policy, although the consignees of products are notified for the purpose of enabling them to inform physicians and others responsible for the care of product recipients.

The policy of the European Community has been to not withdraw or quarantine plasma derived product that originated from a person with CJD.

Neither Australia nor New Zealand have formal policy documents. At this time, neither country is notifying patients of their exposure to blood from a person with CJD nor systematically removing persons with CJD from the donor pool. In Canada, a Health Protection Branch Information Leaflet, October 28, 1995 revised November 1, 1995, stipulated that products would be removed from the market when they are identified as being for a person at risk for CJD. Manufacturers are required to notify the hospital or other agency if blood is

determined to have been donated by a person with CJD, to permit notification of recipients as considered appropriate.

The UK position

At a special meeting of the UK Transfusion Services to discuss the possible implications of the likely new variant of Creutzfeldt Jakob Disease for UK Transfusion Services (9th April 1996) it was agreed that UK Transfusion Services should take urgent action to ensure that direct questioning of donors in relation to a family history of CJD should be instituted but that it would be inappropriate to consider extending current donor selection guidelines beyond the regulatory requirements until the position became clearer. It was also agreed that it is essential to ensure that accurate information is obtained to identify whether identified CJD patients have also donated blood and that this would require information to be provided to transfusion services to enable interrogation of donor databases. It was also agreed that there is a need to consider what action should be taken when a new case of CJD is identified in a current or lapsed donor. It was recommended that a form of look-back is instituted to assist in identifying the potential for transmissibility of this agent by blood. It is also required to investigate systematically whether recorded cases of CJD have received transfusions of blood or blood products.

UK proposal for limited CJD look-back

There is no evidence that CJD, in either its classical or new variant forms, is transmitted by blood transfusion. Nevertheless, information in relation to the potential transmissibility of CJD by blood transfusion is very limited. The absence of information severely restricts ability of the transfusion services to provide definitive reassurance that the new variant form of CJD does not provide a threat to the blood supply. Furthermore, further definition of donors who might be at risk of developing CJD is required. Until further evidence is available, it should be assumed that the newly described variant CJD syndrome is a new disease. It is

appropriate to assume that this would behave in a manner analogous to classical CJD. The potential impact of both CJD and the new variant on the safety of the blood supply is at present unclear. Nevertheless, it is obvious that further information must be accumulated for the purpose of planning resources for future care of individuals affected by CJD and for assisting transfusion services in planning future policies and resources.

The UK Transfusion Services are in an ideal situation to help accumulate knowledge about CJD and blood transfusion, both the classical and variant forms.

1. There is now a well established procedure for recipient look-back, i.e. the tracing of patients who received blood from a donor now known to be carrying an infectious agent, put into place in 1995 when hepatitis C look-back commenced. The procedures for look-back are well established at both transfusion centres and hospitals and the procedures will form a basis on which any subsequent look-back, for any potentially transmissible agent, can be superimposed.

2. Twelve cases of new variant type of CJD have been identified in the United Kingdom and one in France. Although the number of cases is currently small, the Health Department will need to be accumulating information about this new variant disease and its potential implications for public health. The potential, or lack of potential, for transmission through blood transfusion is an integral part of the information required for future planning.

3. The CJD Surveillance Unit in Edinburgh has clinical information in relation to all reported cases of CJD in the UK. This includes information on the history of blood transfusion and donation in all incident cases since 1990 and similar information is available for England and Wales for cases identified in the period 1980-84.

It is proposed that a limited look-back programme would be conducted by the UK Transfusion Services in collaboration with the CJD Surveillance Unit. A key element to this proposal will be the exchange of donor/patient information only between the UK Transfusion Services and the CJD Surveillance Unit. The CJD Surveillance Unit would pass, in confidence, to the Transfusion Services the identity of CJD patients who have ever donated blood. The Transfusion Services will then, with the aid of the look-back protocol, obtain information from hospitals about the fate of individual donations from such donors. The information would include the identity of any recipient know to have received blood from such a case. The details of the recipient would then be passed back to the CJD Surveillance Unit, which could then check these names against the CJD register to ascertain whether any of the recipients are know to have died of CJD (appendix 1). A further check on the OPCS register could be included, to ascertain whether any of these cases could possibly be linked to CJD , although not notified to the CJD register.

It is recommended that the limited look-back would take place without notification of the recipient. The reasons are as follows:

1. There is no screening test available which can detect the possibility of an individual being susceptible to development to CJD in the future.

2. There is no diagnostic test available to detect whether an individual has been infected with the agent which causes CJD.

3. The diagnosis of CJD can only be made with certainty by examination of pathology specimens post-mortem.

4. There is no intervention which can be offered to individuals detected to be at risk of developing disease, or to those who have already developed symptomatic disease.

For all the above reasons, it is considered unethical to notify any individual who has received blood from a donor who subsequently developed CJD. Furthermore, to avoid a possible compromising situation for hospital staff, it is recommended that the reason for the look-back enquiry is not stated anywhere on look-back documentation. For public health purposes, it would be necessary to distinguish the new variant form of CJD from the classical cases. The need to establish transmission or lack of it for the new variant form will be very urgent if there is evidence of an epidemic. The look-back procedure would therefore be crucially important in this case.

It should be noted that, should there be any change in the capacity to diagnose the disease, or if any intervention becomes available in the future, then the transfusion services should have in place a mechanism for contacting the identified recipients.

Detailed information on previous history of blood transfusion and donation is available from the CJD Surveillance Unit. It may be possible to identify all donations given to the recipient, including product batch numbers where fractionated blood products are concerned. These details would then be passed to the Transfusion Services, who would carry out a standard investigation linking these donations to named donors. The identity of these donors would also be passed to the CJD Surveillance Unit, for possible linkage between donors and recipients (appendix 2).

The proposed two way limited CJD look-back study would have the potential to provide:

1. Information on any linkage between donors and recipients.

2. The accrual of data relating to the number of donations originating from donors subsequently identified as suffering from CJD, and how many units have not resulted in development of CJD in the recipient.

Issues arising out of the look-back proposal

1. Confidentiality.

   There is a duty of confidentiality owed to individual donors who have been involved with the blood transfusion services. There is no standard consent by donors to pass on personal medical information to other parts of the NHS. The exchange of information between the CJD unit and the transfusion services would therefore need to be considered in the light of this lack of consent.

   The CJD Unit has a duty of confidentiality to patients and their relatives who have provided detailed information including history of blood donation and transfusion. There is no standard consent from relatives of patients to pass on personal medical information to other parts of the NHS. The exchange of information between the CJD Unit and the transfusion services would therefore need to be considered in the light of this lack of consent.

2. Exclusion of donors considered at risk of developing CJD.

   The transfusion services must exercise a high level of suspicion about possible transmissibility of CJD by blood and err on the side of caution in deciding whether to accept donations from individuals believed to be at risk of developing CJD. To wait until a causal connection is established on a scientific basis may not be regarded as acting with reasonable care. Thus, decisions about selection of donors must not be delayed pending results of the limited look-back, but must be taken in the light of current knowledge and guidelines.

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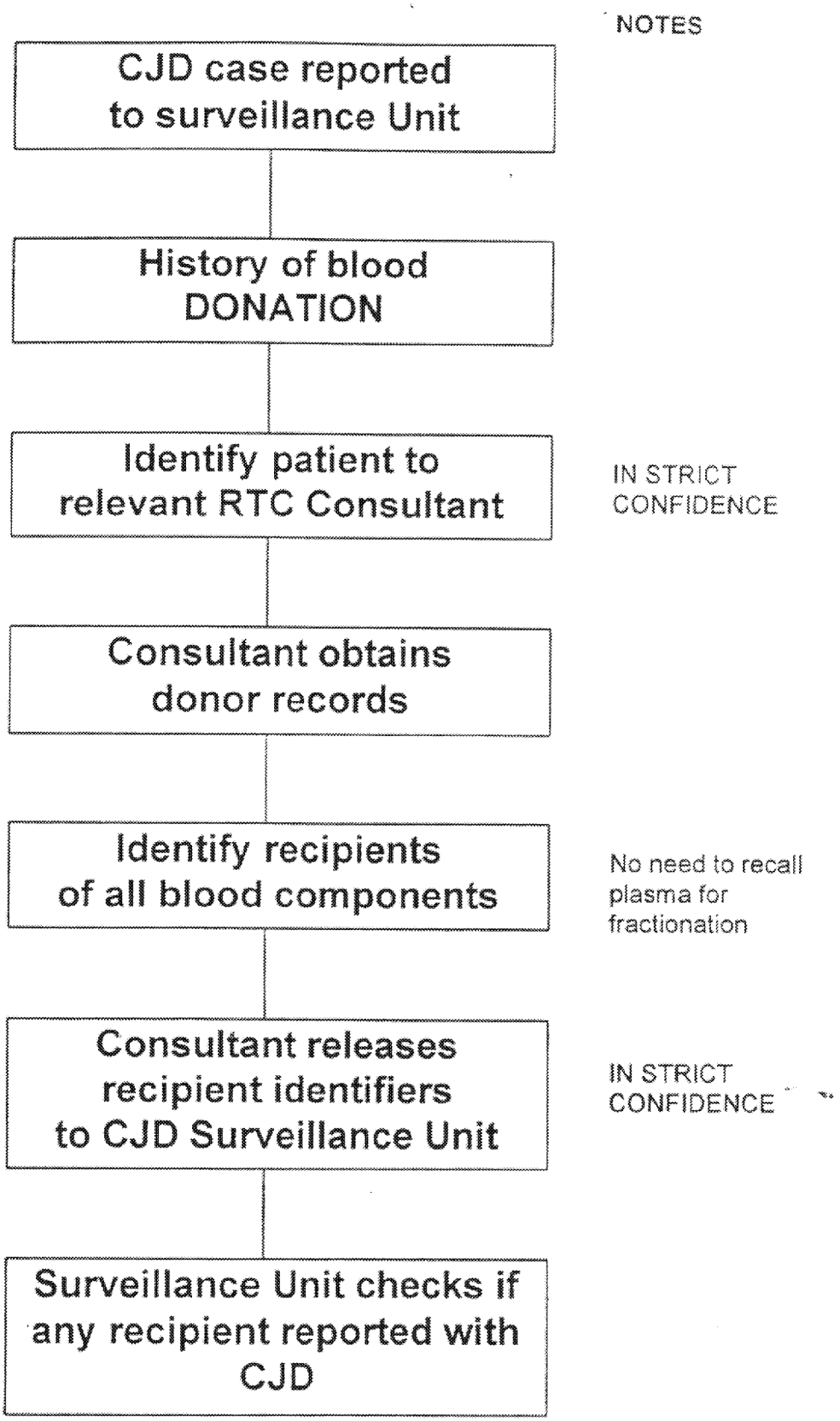
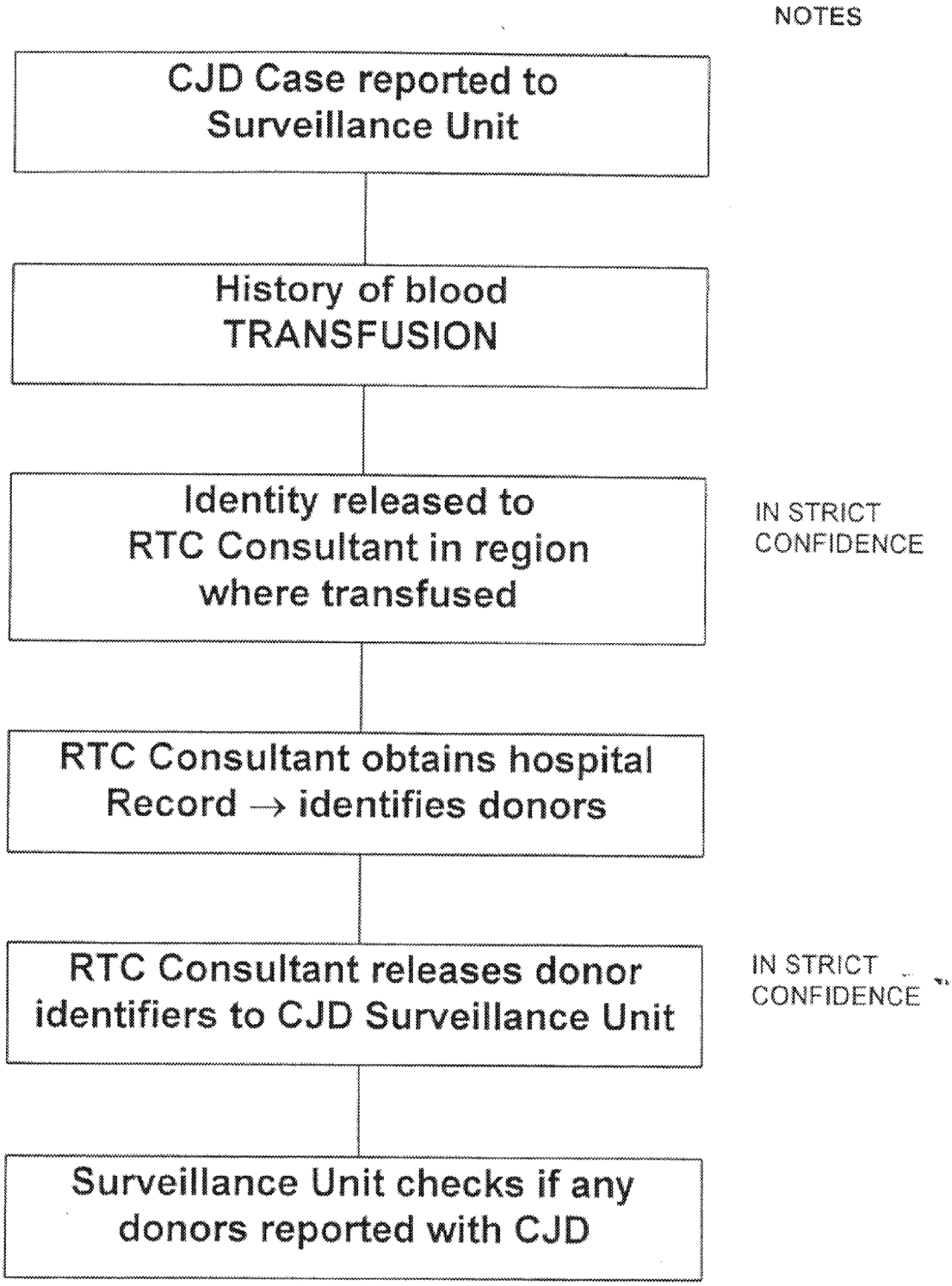
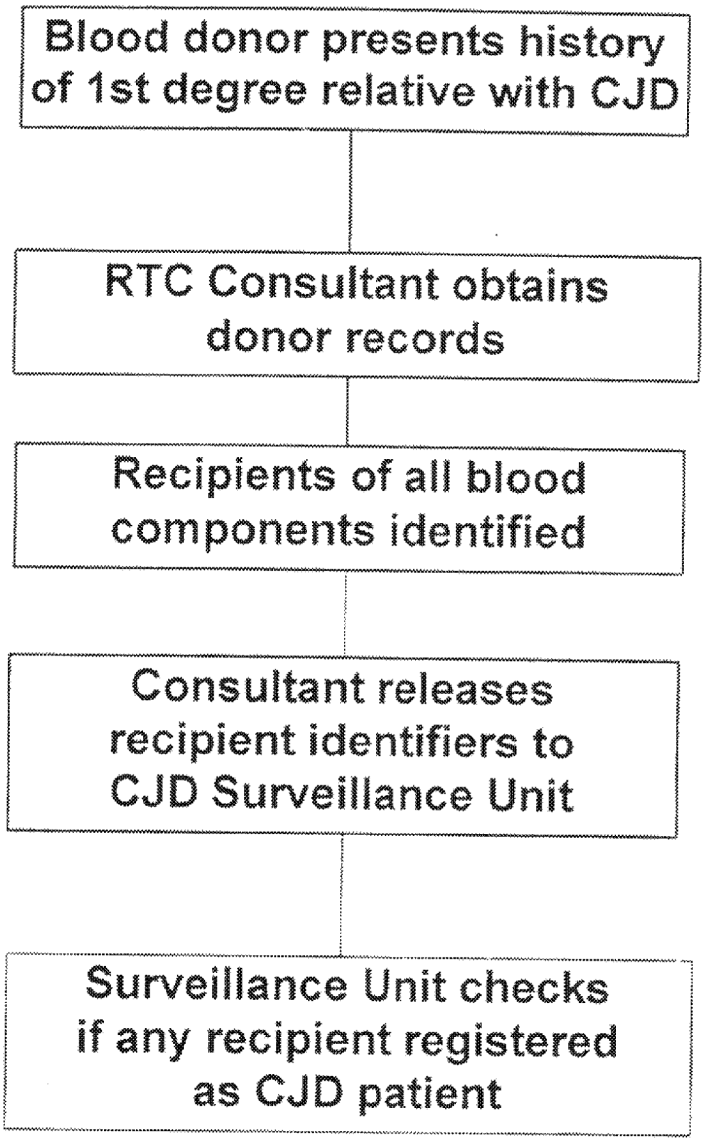
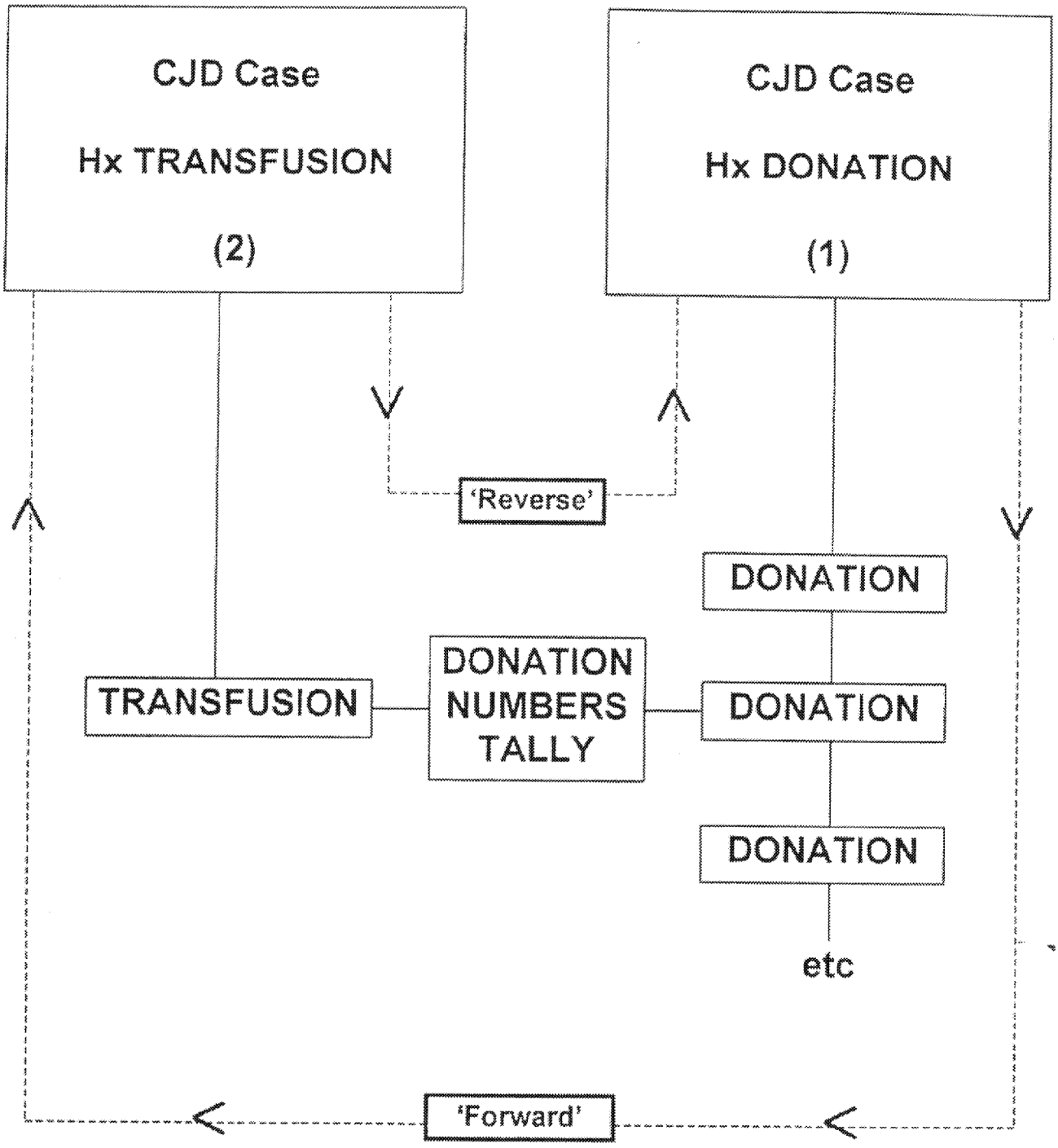


CJD LOOKBACK - (2) 'Reverse'



CJD LOOKBACK - (3) 'Familial Cases'




CJD Case
Hx TRANSFUSION
(2)
CJD Case
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(1)
'Reverse'
DONATION
DONATION NUMBERS TALLY
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DONATION
DONATION
etc
'Forward'