Appendix 2

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Clinical Surveillance Study of

SNBTS Factor VIII/IX Concentrates

Participating Centres

Aberdeen
Belfast
Dundee
Edinburgh
Glasgow (GRI + Yorkhill)
Inverness

23rd February 1989.

Co-ordinator: Dr. C.A. Ludlam.

INTRODUCTION

This surveillance study is primarily designed to assess the safety of SNBTS factor VIII/IX concentrates with respect to transmission of potentially infectious viruses. The protocol is based on the International Committee of Thrombosis and Haemostasis recommendations but entry criteria have been broadened and follow up more prolonged in certain circumstances.

The primary aim of this study is to assess HIV and Non-A Non-B virus transmission by factor VIII/IX concentrates. Evidence will also be sought of parovirus transmission; this is of particularly interest because it is a heat stable virus.

A secondary aim of the study protocol is to allow the collection of lymphocyte subset numbers where these can be readily measured locally.

Blood samples will be collected before infusion of factor VIII/IX concentrate and serially thereafter. The frequency of sampling decreases with time but it is envisaged that the patients should be followed up for at least 2 years after the initial infusion. Ideally a study such as this should be undertaken only in previously untransfused patients (PUPs) but the number of such individuals in Scotland is likely to be small within any one year and it is therefore proposed to include individuals who have only been transfused with single donation products eg cryoprecipitate as well. The data will be analysed separately for PUPs (Group 1) and those who have previously received unfractionated blood products (Group 2).

ELIGIBILITY

Inclusion Criteria

1. Physician believes factor VIII/IX concentrate is necessary therapy and that SNBTS factor VIII/IX is at least as acceptable as any other available blood product.
2. Patients of any age and either sex may be entered.

Exclusion Criteria

1. Patients who have previously been transfused with fractionated pooled plasma products, ie factor VIII or IX concentrates.
2. Patients who are known to have liver dysfunction ie to have abnormality of liver function on routine testing at entry or clinical evidence of chronic liver disease.
3. Serologically positive for anti-HIV, HBsAg, anti HBc or anti-HBs (unless due to vaccination).
4. Patients at risk of HIV infection other than from blood products.
5. Patients with a known history of alcohol abuse.
6. Patients who are unlikely to be available for at least six months follow up.

Number of Patients

Up to 60 patients will be enrolled.

Therapy

This will be with SNBTS factor VIII/IX concentrates which have been dry heated to 80°C for 72 hours. There are no dedicated batches of concentrate reserved for the study.

SAMPLE COLLECTION ARRANGEMENTS

Prior to Therapy

1. For emergency treatment take a single blood sample immediately before infusion of factor VIII/IX concentrate. If possible an additional pre-treatment blood sample should be collected some time before entry for an elective procedure.

2. Give first injection of vaccine for Hepatitis B if not known to be immune.

Blood Samples

All samples will be analysed locally

At Entry:

1. LFTs including ALT and GGT
2. Serum stored (5 ml, for children < 5 yrs - 1 ml)
3. Virology (HAV, HBV, EBV, CMV, HIV and parvovirus)
4. Lymphocyte subsets(optional)

Follow Up Samples

For the first four weeks weekly samples will be collected except for small children who will have a single two week sample. Thereafter samples will be procured fortnightly for sixteen weeks then monthly until 26 weeks after the last infusion or for a total of two years (whichever is the shorter period from the time of first infusion).

Follow Up Samples:

1. LFTs including ALT and GGT. (If ALT not available locally measure AST immediately and store aliquot at -70°C for ALT measurement later).

2, Serum stored (5 ml, for children < 5 years - 1 ml).

At six monthly intervals and at Exit

1. LFTs including GGT
2. Serum stored (5 ml)
3. Virology (HAV, HBV, EBV, CMV, HIV and parvovirus)
4. Lymphocyte subsets (optional)

If ALT (or AST)> 50% over local normal Range

Immediately

1. Retest sample locally
2. Recall patient for further sample. If ALT(AST) within normal range no further action required.

   If ALT (AST)above normal range

   (a) continue to sample weekly until diagnosis of hepatitis confirmed or refuted.

   (b) Full clinical history and examination

   (Check list eg Alcohol
   Drugs
   Contact with an individual suffering from hepatitis or carrier
   Abroad
   Contact with blood products
   Parenteral drug abuse
   Tattoo)

   (c) Virology to be undertaken locally. If patient develops hepatitis serum sample to be sent to a Virology Reference Laboratory.

   (d) Inform Data Collection Centre by telephone and send written confirmation by first class post.

Definition of Hepatitis

Hepatitis is diagnosed by finding an ALT level greater than 2 and a half times the upper limit of the normal range in two samples taken more than 14 days apart.

Documentation

1. Entry Registration Form(Form A) should be completed as soon as a potentially suitable patient is identified and sent to the Data Collection Centre.
2. Report of Infusion Form(Form B) should be completed on each occasion when patient receives factor VIII/IX concentrate and any other blood product and sent to the Data Collection Centre immediately.
3. Liver Function Test Report Form(Form C) should be completed and sent to Data Collection Centre immediately the results of each blood sample are known.
4. Virology Report Form(Form D) should be completed retrospectively for each patient at time of entry and six monthly thereafter.

Analysis of Data

The role of formal statistical inference in all studies of this kind should be very limited. With 60 patients randomly selected, if no side effects are seen, we can state with 95% confidence that the 'population' side effect rate does not exceed 5%. This type of statement will commonly be quoted in a protocol of this kind, but it is misleading. The patients are in no way a random sample, as they are seen over a short period of time, and in consequence will be receiving a limited number of batches of the product being tested. In a situation where batch variability may be important, conventional analysis will therefore give over-optimistic confidence intervals. With side effects expected to

be rare, no useful statistical inferences will be obtained on batch variability. Therefore, we believe that the best approach will be to report the data obtained descriptively.

In the presentation of results it will be important to stratify according to whether or not the patient has been previously untreated with blood products (Group 1) or previously treated (Group 2). In Group 2 early evidence of non-A non-B hepatitis may be a consequence of previous treatment and all relevant previous treatment would be included in the presentation.
Throughout the study, any incident of non-A non-B hepatitis, or other possible major side effect will lead to a review of the data.

Legal Considerations

1. For current factor VIII (Z8) and factor IX (Defix) the study is covered by ABPI guidelines.

2. For new SNBTS Factor VIII and IX products a CTX will be obtained by SNBTS and the study will not start until this is available and written assurance from SHHD is received that ABPI Guidelines cover will apply.

3. Approval must be obtained from local ethics committees (to include children).

4. All episodes of hepatitis will be reported to the Communicable Disease (Scotland) Unit who will investigate and report to the Co-ordinator and Chairman of the Independent Data Review Committee.

5. /

5. The documentation of two cases of non-A non-B hepatitis transmission will lead to a full review of the use of the implicated product.

6. An Independent Data Review Committee will be established. All episodes of Hepatitis will be reported to the Chairman of this group who will take what action is considered appropriate.

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Form A

REGISTRATION FORM

Surname ..... Forename ..... DOB .....

Diagnosis ..... Basal Factor Level .....

Haemophilia Centre .....

Previous blood product treatment Yes/No

If Yes - details so far as possible

PRODUCT	DOSES	HOSPITAL	DATE
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....

Is there a history of clinical hepatitis Yes/No

Details: .....

Is the patient taking any drugs? .....

Reporting Doctor .....

Date ..... Signature .....

Complete this form as soon as a potentially suitable patient has been identified and send a photocopy immediately to Data Collection Centre, c/o Dr. R.R.C. Stewart, S.N.B.T.S. Headquarters Unit, 2 Forrest Road, Edinburgh EH1 2QN by first class post.

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Form B

REPORT OF BLOOD PRODUCT INFUSION

Surname .....Forename .....DOB.....

Haemophilia Centre .....

This is the first/subsequent infusion

(delete as appropriate)

PRODUCT	BATCH NO.	DOSE	DATE	TIME
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....
.....	.....	.....	.....	.....

Reporting Doctor ..... Signature .....

Date .....

Complete this form as soon as a potentially suitable patient has been identified and send a photocopy immediately to the Data Collection Centre, c/o Dr. R.C.C. Stewart, S.N.B.T.S. Headquarters Unit, 2 Forrest Road, Edinburgh EH1 2QN. by first class post.

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Form C

REPORT OF LIVER FUNCTION TESTS

Surname ..... Forename .....

Haemophilia Centre .....

Intended sampling date .....

Actual sampling date .....

Attach xerox copy of laboratory report or -

	RESULT	LOCAL NORMAL RANGE
Bilirubin	.....	....
Alkaline phosphatase	.....	....
Alanine amino Transferase	.....	....
Gamma glutamyltransferase	.....	....
Aspartate aminotransferase	.....	....

Lymphocyte subsets - will result be available? Yes/No

Has a sample of serum (5 ml or 1ml for children) been stored? Yes/No

Reporting Doctor .....

Date ..... Signature .....

Complete this form as soon as a potentially suitable patient has been identified and send a photocopy immediately to Data Collection Centre, c/o Dr R. C. C. Stewart, S.N.B.T.S. Headquarters Unit, 2 Forrest Road, Edinburgh EH1 2QN by first class post.

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Form D

VIROLOGY REPORT FORM

Surname ..... Forename .....DOB .....

Haemophilia Centre .....

Date of Sample .....

Results

Anti HIV	Positive/Negative
HBsAg	Positive/Negative
Anti HBs	Positive/Negative
Anti CMV	Positive/Negative
Anti EBV	Positive/Negative
Anti HHV	Positive/Negative
Anti Parvovirus	Positive/Negative

Reporting Doctor .....

Date ..... Signature .....

Complete this form as soon as a potentially suitable patient has been identified and send a photocopy immediately to Data Collection Centre, c/o Dr R. C. C. Stewart, S.N.B.T.S. Headquarters Unit, 2 Forrest Road, Edinburgh EH1 2QN by first class post.

Scotland/Northern Ireland Haemophilia Centre Directors

Patient information for study of Scottish Blood Transfusion Service factor VIII/IX concentrate.

1. Explanation of the purpose of this research

Either to prevent or stop bleeding, you/your child need(s) treatment with factor VIII or IX concentrate. All factor VIII and IX concentrates, whether made by the NHS or imported from abroad, are prepared from plasma obtained from several thousand donors. Although all donors are carefully screened before their plasma is accepted, and all concentrates are treated to destroy any HIV (AIDS virus), the risk of transmission of other viruses has not been entirely eliminated.

The main problem which remains to be overcome is to minimise the chance of transmission of the virus which causes non A, non B hepatitis (NANBH). With this objective the factor VIII concentrate which is being used in this study has been purified and heat treated by new methods. It is expected to have a reduced risk of virus transmission. The only way to prove this, however, is to carry out regular blood tests in people who have received treatment with this new concentrate. Because people who have never previously been treated with concentrate (such as you/your child) are thought to be at most risk of NANBH, the study is at present limited to this group.

2. Plan of the study

Before treatment with factor VIII, a blood sample will be taken and the first of 3 injections of a course of hepatitis B vaccine will be offered (if you/your child have not previously been vaccinated against hepatitis B). After treatment with factor VIII or IX, a blood sample and brief clinical examination will be needed at least every 2 weeks for 4 months and then once a month

for a further 2 months. If you receive further treatments blood samples will be further collected at monthly intervals for at least six months after the last treatment.

3. Alternative possibilities for treatment

Why treatments other than factor VIII or IX concentrate are not considered to be appropriate in you or your child's case will be explained. If you choose not to participate in this study, we shall in any event recommend frequent clinical and blood test follow-up.

4. Potential benefits

Judging from the freedom from ill-effects observed with this type of material, and on the basis of preliminary studies it is expected to have fewer side effects. If this is confirmed both you/your child and other haemophilia patients will benefit.

5. Potential risk and discomforts

All products made from human blood carry a risk of transmission of infection. Although experience with this type of concentrate has so far been very good a thorough study in many patients in different hospitals is required and until this is done it cannot be assumed to be without risk. Like other factor VIII concentrates, it may occasionally cause transfusion reactions. The need for frequent blood tests after treatment may be inconvenient and mildly uncomfortable.

6. Any questions you may have

Any of the medical or nursing staff of the Haemophilia Centre who are involved in this study, will be glad to answer any questions you may have, now and at any time in the future.

7. Confidentiality

Records relating to this study will be kept in the Haemophilia Centre and will be made available to professional staff involved in the study. Copies of records, with names removed and code

numbers inserted, will be made available to the Protein Fractionation Centre in Edinburgh (the manufacturer of the concentrate) and also to collaborating investigators in other hospitals. It is possible that officials from the Departments of Health may also wish to inspect the records. At the end of the study, results will be reported in a scientific journal. The identity of patients will not be disclosed in this report, which will be given to you on request after it has been published.

8. Reimbursement of expenses

Any reasonable expenses you may incur as a result of participation in this study will be reimbursed.

9. Your right not to participate

You are free not to participate in this study. If you do agree to participate you may withdraw your consent and discontinue participation at any time without jeopardising your medical care in any way. We shall let you know the findings of the study as it progresses, so you will always be aware of any new information which becomes available which may affect your decision to continue participation.

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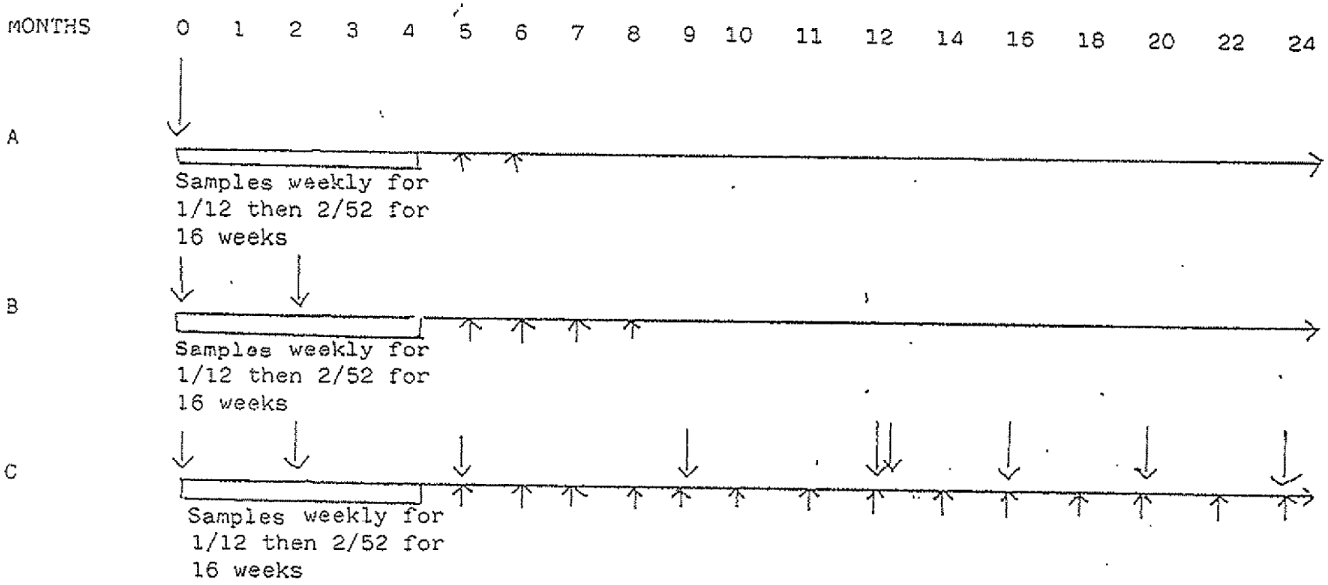

NB Follow up is for 6 months after last infusion or 2 years whichever is the shorter period.