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CLINICAL EVALUATION OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA (`OCTAPLAS`) IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA, AND IN CORRECTION OF COAGULOPATHY DUE TO EITHER WARFARIN, LIVER DISEASE OR LIVER TRANSPLANTATION

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CLINICAL EVALUATION OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA (`OCTAPLAS`) IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA, AND IN CORRECTION OF COAGULOPATHY DUE TO EITHER WARFARIN, LIVER DISEASE OR LIVER TRANSPLANTATION

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FINAL VERSION REVISED JANUARY 1994: VERSION 6. PLEASE DISCARD EARLIER DRAFTS

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ABSTRACT

This is a Phase II prospective, randomised, single blind study in hospital patients over 6 months, designed to examine the tolerance, efficacy, and viral safety of solvent/ detergent treated ABO compatible fresh frozen plasma (SD FFP) in the following clinical settings:-

1. ~~Patients requiring immediate reversal of warfarin therapy (n = 40).~~ OK out

2. Patients requiring reversal of the coagulopathy of liver disease (n = 50).

3. Liver transplants (n = 24).

4. Patients requiring plasma infusion or plasma exchange for the management of newly diagnosed TTP (n = 6).

The study will examine clinical tolerance and safety at both low and high dosage, efficacy in correction of coagulopathy, and effectiveness in prevention of transmission of HIV, hepatitis B and HCV. Because Hepatitis A is not destroyed by SD treatment, anti-HAV status will also be assessed. Patients in groups 1, 2 and 3 will be randomised, but not in a blinded fashion, to receive 400-800 mls of either standard FFP, or SD FFP. Patients in group 4 (newly diagnosed TTP) will NOT be randomised, but all will receive SD FFP 3 litres daily as clinically necessary for up to 14 days.

Donor plasma for both arms of the study will be collected in the UK by apheresis from voluntary donors, and screened for hepatitis B Surface antigen, anti-HIV 1 + 2, and anti-HCV. Plasma in the control arm of the study will also be collected by apheresis. Plasma intended for SD treatment will be pooled to produce 2 x 200 litre pools (1 group O and 1 group A).

SD treatment will be with tri(n-butyl)phosphate (TNBP) and Triton X-100 according to Octapharma Licence numbers 9554 and 9557, (German Certificate of Pharmaceutical Products), Dusseldorf 1991. Following treatment, plasma will be dispensed into 200ml packs, and stored at -30°C.

Evaluation will include:-

1. Monitoring of pulse, blood pressure, temperature, and skin reactions during and after the infusion.

2. In warfarin reversal and liver disease groups - INR or prothrombin time and assays of fibrinogen, factors II, VII and protein C, pre-, 30 minutes and 24 hours post infusion.

3. In liver transplant patients, assays of fibrinogen, factors II, V, VII, VIII and protein C pre-, 30 minutes and 24 hours post-infusion.

4. In TTP patients - platelet count, presence of red cell fragments on blood film, lactate dehydrogenase and creatinine assays, multimeric analysis of von Willebrand factor.

5. In all patients - anti-HIV 1 + 2, anti-hepatitis B core antigen, anti-HCV and anti-HAV before and 6 months after infusion.

1.0 INTRODUCTION

1.1 Clinical Usage of Fresh Frozen Plasma

Fresh frozen plasma (FFP) is the standard blood product used for the correction of generalised clotting factor deficiencies, as seen in disseminated intravascular coagulation, warfarin excess, or liver disease[1,2]. In addition, the product has specific uses in certain other conditions, such as thrombotic thrombocytopenic purpura, when, in conjunction with plasma exchange, up to 3 litres may be given daily[3]. Approximately 220,000 units per year are transfused annually in the United Kingdom.

1.2 Viral Safety

The viral safety of FFP currently depends entirely on donor selection and screening of donations for Hepatitis B surface antigen, and antibodies to HIV 1 and 2, and HCV. There is thus a small but finite risk of viral transmission by this product, as till now there has been no way of achieving viral killing in FFP. The risks of infection are estimated at 1 in 25,000 for HBV, 1 in 300,000 for HIV-1, negligible for HIV-2 and 1 in 1000 for HCV [4,5]. These estimates come from American studies; the risks in the UK are probably in the order of 1:100,000 for HBV, 1:1,000,000 for HIV-1, negligible for HIV-2, and 1:5,000 for HCV. The actual risk for HCV transmission is not yet determined. It was reduced by the introduction of second generation screening assays but these assays may not yet be of optimal sensitivity.

1.3 Solvent/Detergent Method of Virus Killing

1.31 Solvent/Detergent Treatment of Clotting Factor Concentrates

Concentrates of the coagulation factors VIII and IX became significantly safer once methods of sterilising them without unacceptable loss of functional activity became available. One method which has been successfully developed is the treatment of concentrates with an organic solvent, tri (n-butyl) phosphate (TNBP) and detergent (sodium cholate, Tween 80 or Triton X-100), followed by removal of the solvent/ detergent mixture by passage over a resin column[6]. This method has been shown to inactivate very large quantities of HBV, HCV, and HIV, by dissolving their lipid envelope. There is little or no loss of coagulation factor activity in clotting factor concentrates[7], and several clinical studies in haemophiliacs have affirmed the safety and acceptability of these products [8]. Some non enveloped viruses such as parvoviruses and hepatitis A could still be transmitted but their frequency in donor blood is extremely low. incidence of anti-HB in new donor plasma pools? ↑

1.32 Toxicity

1.321 Animal Studies

Final concentrations of TNBP in clotting factor concentrates have been controlled within tightly set specifications set by both

manufacturers and regulatory bodies, taking into account both volume infused and frequency of infusion. Factor VIII concentrates contain <5ppm TNBP[9]. These levels equate to 1:500-1:25,000 below the LD_{50} for mice [10], and rabbit studies have also shown absence of toxicity on repeated high dose exposure over 13 weeks[9].

1.322 Human Exposure

Factor VIII concentrates prepared at the New York Blood Centre with TNBP were licensed by the Food and Drug Administration in 1985, so many haemophiliacs in the New York area have received exclusively or principally TNBP-treated products for roughly 6 years. Worldwide, the equivalent of 2 million 1000-unit doses have been administered, equating to 20,000 man-years of treatment at 100,000 units per man-year (Watlkevicz 1991, cited in 9). No adverse effects have been noted during this 6-year period.

1.33 Solvent/Detergent Treatment of Fresh Frozen Plasma

The same solvent/detergent process has now been applied to FFP for direct clinical use, and has been shown to kill the marker lipid-enveloped vesicular stomatitis virus and Sindbis virus even more rapidly than in clotting factor concentrate, as well as HIV (> 7 log kill), HBV (≤ 5 log kill) and HCV (≤ 4 log kill)[11]. In this study, loss of coagulation factor activity was 13%, 12%, 1% and zero for factors V, VIII, IX and XI respectively, and there was no evidence of neoantigen formation.

An SD virus-inactivated plasma product, manufactured under the license of Octapharma by DRK (German Red Cross) Hagen, has been sold in Germany for the last 18 months (more than 80,000 units). No transmission of HIV1/HIV2, non A non B hepatitis (including hepatitis C) or hepatitis B have been reported. In addition, clinical experience and results from ongoing and finished clinical trials, using SD-virus inactivated plasma products manufactured according to the NYBC method and under Octapharma's licence, demonstrate a high degree of tolerability, comparable with normal fresh frozen plasma.

It is proposed to evaluate this material in prospective randomised studies in warfarin reversal and correction of coagulopathy prior to liver biopsy, and in an open (non-randomised) study in thrombotic thrombocytopenic purpura (TTP).

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.11 A Phase II, prospective randomised single-blind study to evaluate the tolerance, clinical efficacy and viral safety of SDFFP in the clinical settings of:

- 2.111 Urgent reversal of warfarin
- 2.112 Management of the coagulopathy of liver disease.
- 2.113 Liver transplantation.
- 2.114 Management of newly diagnosed TTP requiring either plasma infusion or plasma exchange.

2.2 Secondary Objectives

2.21 To examine the efficacy of SDFFP in reversing pre-existing laboratory abnormalities as follows:-

- 2.211 In warfarin treatment, elevated international normalised ratio (INR) and low factors II, VII and protein C.
- 2.212 In liver disease patients, prolonged prothrombin time and low factors II, VII and protein C.
- 2.213 In liver transplant patients, low fibrinogen and factors II, V, VII, VIII and protein C.
- 2.214 In newly diagnosed TTP, low platelet count, red cell fragmentation on blood film, elevated lactate dehydrogenase and abnormalities of von Willebrand factor multimers.

3.0 STUDY DESIGN

This is a phase II clinical trial on a limited number of patients to assess therapeutic safety and efficacy.

3.1 Patient population and study numbers:

A) Patients requiring urgent reversal of warfarin therapy (n = 40, or the number recruited in a 6 month period up to 40).

B) Patients requiring correction of a prolonged prothrombin time due to liver disease (n = 50, or the number recruited in a 6 month period up to 50).

C) Liver transplants (*n* = 24)

Patients in groups A, B and C will be randomised, but randomisation will be separate for each group. Randomisation will be between 400-800 mls of standard FFP and 400-800 mls of SDFFP.

D) Patients requiring plasma infusion or exchange for newly diagnosed TTP (n = 6, or the number recruited in a 6 month period up to 6).

TTP patients will NOT be randomised; all will receive SDFFP, up to 3 litres daily, either alone, or as part of a plasma exchange procedure.

This will be a multi-centre study, involving 3 Regional Transfusion Centres, and 1-5 hospitals in each region. Patients will be randomised within each participating hospital to avoid bias and prevent delays in initiation of therapy. Local Ethical Committee approval will be required at all centres.

It is not proposed to carry out a double blinded study. However, the study will be single blinded in that patients will not know which material they will receive. This will be made clear in the Consent Form (Appendix 1).

If the study numbers have not been achieved by six months, the Sponsors and Clinical Investigators will review accrual rates and a decision taken whether to extend the trial for an additional period of not more than four months.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

4.11 Patients presenting with EITHER

4.111 Warfarin treatment requiring immediate correction with FFP. This will be a clinical decision, and will include patients with frank haemorrhage or at high risk of haemorrhage.

OR

4.112 Liver disease, with a prothrombin time greater than 4 seconds prolonged i.e. >4 seconds longer than the control, in whom replacement with FFP is considered necessary.

OR

4.113 Patients undergoing orthoptic liver transplantation.

4.114 Newly diagnosed TTP requiring treatment with plasma infusion or plasma exchange.

4.12 Patients must be aged over 18.

4.13 Patients must be group A or O.

4.14 Patients must have read the information sheet and have signed the informed consent form. Consent for anti-HIV testing will be requested separately; patients who refuse consent for this will still be included in the study, and all other parameters monitored **except** anti-HIV status. Patients for whom next-of-kin give consent will not have HIV status assessed.

4.15 The Ethical Committee of each hospital must have approved the study.

4.2 Exclusion Criteria

4.21 Patients under 18.

4.22 Pregnant women.

4.23 Patients of B or AB blood groups.

4.24 Patients who have previously reacted to FFP.

4.25 Patients in warfarin or liver disease groups who have received blood products within the previous 6 months, because of the possibility that viral sero-conversion might relate to these products and not to the FFP.

4.26 Rh negative patients if anti-D is present.

? females in child bearing age group.

Notes

1. Liver transplant and TTP patients who have received blood products within the previous 6 months CAN be entered, but the information should be documented on the entry form.

2. The viral status of patients will not usually be known at the time of entry and randomisation. If the patient is known to be seropositive for any viral markers prior to the trial, they may still be entered and evaluated, but the information must be forwarded to the trial co-ordinator.

3. SDFFP is not Rhesus specific. Infusion of Rh positive FFP into a Rh negative individual has caused boosting of pre-existing anti-D, but not primary immunisation. Thus Rh negative patients may be entered provided they do not have anti-D. For Rh negative patients randomised to receive standard FFP, participating centres should follow their usual practice with regard to Rh specificity.

are you sure about this →

5.0 SOURCE AND MANAGEMENT OF PATIENTS

5.1 Number of Patients

5.11 Warfarin Reversal
Forty patients requiring FFP for urgent reversal of warfarin either because of excessive treatment, or to correct an INR in the therapeutic range to allow an operative procedure.

5.12 Coagulopathy of Liver Disease
Fifty patients requiring correction of a prolonged prothrombin due to liver disease will be recruited.

5.13 Liver Transplants
Twenty-four patients requiring correction of the coagulopathy of liver transplantation will be recruited.

5.14 Newly Diagnosed TTP
Six patients requiring plasma infusion or plasma exchange for TTP will be recruited.

5.2 Source of Patients

Patients will be hospital in-patients in the East Anglia, West Midlands and Yorkshire Regions of England.

5.3 Management of Patients

For a summary of procedures and documentation see Appendix 2.

5.31 Entry of Patients

Patients will be entered into the study by telephone or fax to the Trial Co-ordinator, Dr. Lorna Williamson (telephone 0223 245921, extension 276; fax 0223 411618), giving patient's name, hospital number, trial number, and product allocation. All patients will have a verbal and written explanation of the study by a physician (see Appendix 1), and written informed consent will be obtained. This can be obtained from the next of kin if the patient is too ill to consent. Separate written consent will be required for anti-HIV testing (see Appendix 1), but where the next of kin gives consent for entry to the study, HIV testing will not be performed. During randomisation, each patient will be allocated a unique trial number for the study.

5.32 Randomisation of Patients

Separate randomisation of patients in WARFARIN REVERSAL, LIVER DISEASE AND LIVER TRANSPLANT GROUPS will take place within each hospital to avoid bias and prevent delays in initiation of therapy. On identification of a suitable patient requiring FFP, randomisation will be performed by Blood Bank staff by opening an envelope containing a unique patient number and arm of study allocated. Each hospital will be provided by the Trial Co-ordinator with a number of coded envelopes corresponding to the anticipated number of entries. These will be pre-allocated using a computer-generated random numbers list. Patients will be randomised to receive either standard FFP or SDFFP.
PATIENTS IN THE TTP GROUP WILL NOT BE RANDOMISED; ALL PATIENTS WILL RECEIVE SDFFP

5.33 Withdrawal of Patients

Patients may be withdrawn from the study before therapy and sampling are complete if:-

a) there is a clinically unacceptable reaction to or side-effect of the product;

b) Newly diagnosed TTP patients, who will all receive SDFFP, may be withdrawn at the clinician's discretion if there is no response to therapy after four days.

FULL TRIAL DATA ON SUCH PATIENTS MUST BE RETURNED TO THE TRIAL CO-ORDINATOR

Patients who have received any FFP as part of the study must be included in the data analysis, even if they have been only partially treated.

6.0 STUDY TREATMENT

6.1 Source and Treatment of Plasma

6.11 Collection and Testing of Plasma

Plasma for both arms of the study will be collected by apheresis from voluntary blood donors of both sexes in the UK and processed according to procedures set out in Schedule 1 (The Plasma Specification) in the Agreement between Octapharma A.G. and the National Blood Authority. Schedule 1 is based on the current `Guidelines for the Blood Transfusion Service in the United Kingdom`[12].
It is recognised that the plasma from group A individuals in both the standard and SD FFP groups will have a higher factor VIII level than that of group O donors.

6.12 Solvent Detergent Treatment of Plasma

Plasma intended for SD treatment will be stored at -40°C for up to one month then shipped to Octapharma for treatment at the Bio Products Laboratory, Elstree. The plasma will then be pooled into 2 x 200 litre pools (1 pool each of groups O and A), thus each pool will contain plasma from all 3 participating centres, amounting to approximately 330 donations/pool. The end product will be obtained exclusively from the UK plasma provided for the purpose of this investigation.
Virus inactivation is carried out by a solvent-detergent (SD) technique, using 1% TNBP and 1% Triton X-100 as solvent and detergent reagent respectively. The SD reagents are removed by oil extraction (removes TNBP) and subsequent reverse phase chromatography (Hydrophobic Interaction Chromatography: HIC) on C 18 resin (removes Triton X-100 + residues of TNBP).
The pooled SDFFP will then be dispensed into sterile packs containing 200 mls plasma then transported at -25° C to the U.K. for distribution. Storage thereafter in the UK will be below -30° C. Material from each of the 2 pools (A and O) will be made available to each participating transfusion centre. Because SDFFP does not carry a product licence in the UK, material will be made available on a named-patient basis only with a Clinical Trials Exemption certificate from the Medicines Control Agency. SDFFP will be supplied at the same price as standard FFP.

6.13 Standard FFP

Standard FFP will be collected, processed and tested in the same way as plasma intended for SD treatment, but will not undergo any end product modification. Standard FFP in 400 ml packs will be retained as single packs in the Regional Transfusion Centres at -40°C for up to 9 months. This is **NOT** a pooled product.

6.2 Product Descriptions

6.21 SDFFP

SDFFP, prepared as described in 6.11 and 6.12 above, will be supplied by the National Blood Authority to the Regional Transfusion Centres, from whom hospitals will obtain supplies. The plasma will be supplied in the frozen state and can be stored at ≤-30°C for up to 12 months, -25 to -30° C for up to 6 months, or at -18 to -25°C for up to 3 months. It should be protected from light during storage. The total protein concentration will be 40-60 g/litre (pH 6.5-7.5), and the final concentrations of TNBP and Triton X-100 will be <1ug/ml and <6 ug/ml respectively. This product is NOT Rh specific.

6.22 Standard FFP

Standard FFP, prepared as described in 6.11 and 6.13 above, will be supplied to hospitals in dry ice and stored at -20°C for not more than 3 months prior to use. Each pack of 400 mls will contain the plasma from 1 donor. Rh negative patients must receive Rh negative FFP.

6.3 Administration and Dosage

6.31 SDFFP

SDFFP should be thawed in a water bath, in an outer sealed plastic bag, to a temperature of not greater than 37°C, and administered not more than 2 hours later.

The dose in the warfarin reversal and liver disease groups will be 400-800 mls; this concurs with a recommended dose of 12 - 15 mls/kg over 1-2 hours[2].

If clinically required the physician in charge may repeat the dose using the same product as the initial dose.

If patients in the Warfarin group require vitamin K also, this must be given after the 30 minute post-infusion samples have been taken. This should be recorded on the Case Report Form.

For the liver transplant group, 400 mls will be infused over 5 minutes, and immediately repeated if the prothrombin time has not corrected to within 4 seconds of the control.

For the TTP patients, SDFFP may be given as a plasma infusion or as part of a plasma exchange procedure, at the physician's discretion. The dose will depend on whether plasma infusion or exchange is being performed, and how many plasma exchanges are to be carried out, but up to 3 litre/day for 14 days is permissible.

No drugs or other blood products shall be mixed with the plasma infused as part of the Protocol procedures. All forms of therapy to patients included in the Protocol must be noted on the Case Report Forms during the period of observation.

6.32 Standard FFP

As for SDFFP.

6.4 Possible Adverse Effects

6.41 Standard FFP

FFP has the following well-recognised side effects:

6.411 Allergic reactions - fever, rigors, urticaria, bronchospasm and cardio-respiratory collapse. The incidence of urticaria is 1-3%. The incidence of life-threatening anaphylactic reactions is not known, but could be as high as 1:20,000 transfusions[13].

6.412 Transmission of HIV, HBV and HCV with the same risks as whole blood from the same donor population.

6.413 Fluid overload, if rapid infusion is required.

6.414 Rarely, potent antigranulocyte antibodies may be present, which can cause leucocyte aggregation in pulmonary vessels and acute pulmonary injury[14], a syndrome known as Transfusion Related Acute Lung Injury.

6.415 Recent reports have suggested that plasma infusion may cause immune suppression[15].

6.42 SDFFP

As for standard FFP, except that the risks of transmission of lipid-enveloped viruses should be negligible. No particular immediate adverse effects have been reported from residual TNBP and Triton X-100, either in animal studies, or in factor VIII concentrates, where the final concentration is <5 ppm[9].

7.0 CLINICAL MONITORING

The protocol for the clinical and laboratory monitoring is summarised in Appendices 3A (warfarin reversal, liver disease and liver transplantation) and 3B (TTP).

7.1 Temperature

Record prior to, and 30, 60 and 120 minutes, and 4 hours after the start of the infusion. Also, for liver transplant and TTP patients only, a record should be made after 15 minutes.

7.2 Pulse

Record prior to, and 30, 60 and 120 minutes, and 4 hours after the start of the infusion. Also, for liver transplant and TTP patients only, a record should be made after 15 minutes.

7.3 Blood Pressure

Record prior to, and 30, 60 and 120 minutes, and 4 hours after the start of the infusion. Also, for liver transplant and TTP patients only, a record should be made after 15 minutes.

7.4 Skin Changes

Record prior to, and 30, 60 and 120 minutes, and 4 and 24 hours after the start of the infusion. Also, for liver transplant and TTP patients only, a record should be made after 15 minutes.

8.0 LABORATORY MONITORING

8.1 Parameters to be Monitored

8.11 In All Study Groups

Viral serology - anti-HIV 1 + 2, anti-hepatitis B core antigen, anti-HCV and anti-HAV pre-infusion and at 6 months. All tests will be performed on kits approved for use within the NBA.

NOTES

1. Although it is recognised that some seroconversions for HCV can occur between 6 and 12 months after exposure, it is proposed to examine the results of the 6 month post-transfusion samples before making a decision about 12 month testing. If there have been any seroconversions in the SD FFP arm at 6 months, then all patients in this arm will be retested at 12 months.

2. It is appreciated that, prior to development of serological methods for detection of HCV infection, the standard accepted method for the detection of non-A, non-B hepatitis was to measure ALT at 2-weekly intervals. However, second and third generation assays for HCV are now available, and this study is concerned with viral transmission rather than development of clinical hepatitis. Therefore it is not proposed to carry out ALT testing following transfusion.

3. In view of the fact that the SD method does not destroy non lipid coated viruses, all patients will be tested for anti-HAV pre and post infusion.

4. If any patients are found to have seroconverted for any viral marker at 6 or 12 months, a full transfusion history will be documented for the period between FFP treatment and detection of seroconversion.

8.12 In Warfarin Reversal Group

Coagulation parameters - international normalised ratio (INR), partial thromboplastin time with kaolin (PTTK)/ kaolin cephalin clotting time (KCCT), and factors II, VII and protein C prior to, and 30 mins and 24 hours after the completion of the infusion.

8.13 In Liver Disease Group

Coagulation parameters - prothrombin time (PT), PTTK/KCCT, and factors II, VII, and protein C prior to, and 30 mins and 24 hours after completion of the infusion.

8.14 In Liver Transplant Group

Coagulation parameters - fibrinogen, factors II, V, VII, VIII and protein C, prior to and 30 mins and 24 hours after completion of the infusion.

NOTES

1. Correction of coagulopathy will be considered to have occurred if the prothrombin time in the 30 minute sample is 4 seconds or less above the control plasma tested simultaneously.

2. It is not proposed to conduct a formal assessment of half-life of any individual clotting factors.

3. Factor VIII will be measured by a one stage assay on an ACL coagulometer.

8.15 In TTP patients

NOTE - all samples should be taken daily prior to plasma infusion or exchange.

Haematological parameters - haemoglobin, white cell count, platelet count, and blood film to look for red cell fragmentation prior to, and daily till the end of treatment.

Coagulation parameters - prothrombin time and PTTK/KCCT daily. Multimeric analysis of von Willebrand factor to look for ultra-high molecular weight forms. Prior to, and daily until completion of treatment.

Biochemical parameters - lactate dehydrogenase (as a marker of haemolysis), and creatinine prior to, and daily till completion of treatment.

8.2 Handling of Samples

8.21 Performed at Referring Hospital

The following assays may be performed at referring hospitals according to locally agreed sampling protocols with regard to volume and type of sample tube:-

Haemoglobin, white cell count, platelet count, assessment of blood film for red cell fragmentation (TTP only) .
Lactate dehydrogenase and creatinine (TTP only).
INR (International Normalised Ratio) and prothrombin time. Where a prothrombin time has been performed at the referring hospital, the ISI (International Sensitivity Index) of the thromboplastin used should be noted on the case report form. This will allow calculation of an INR and thus correct for differences in thromboplastins between participating hospitals.
KCCT/PTTK.

8.22 Performed Centrally

8.221 Assays of Fibrinogen, Factors II, V, VII, VIII, Protein C and von Willebrand Factor Analysis

A 10 ml citrated sample should be centrifuged and separated as soon after collection as possible, and certainly within 4 hours. Citrated plasma should be stored at -40°C then sent, in dry ice, to the Coagulation Laboratory, Addenbrooke's Hospital NHS Trust, Cambridge (Dr. Trevor Baglin). All samples will be frozen to -70°C and thawed prior to assay.

8.222 Viral Serology

A 10 ml clotted sample should be stored at 4°C then sent to Virology Laboratory, East Anglian Blood Transfusion Centre, Long Road, Cambridge.

An archive serum sample prior to and 6 months after treatment will be held by EABTC at $\leq$-20°C for two years from the date of treatment.

8.223 Samples may be taken into evacuated tubes; it is important that they are filled to the line.

9.0 CLINICAL AND LABORATORY ENDPOINTS

9.1 Adverse Effects

9.11 Pyrexial Reaction
Defined as a rise in temperature of $>1^{\circ}$ C, during or within 4 hours of the infusion.

9.12 Rigors

9.13 Tachycardia
Defined as an increase in pulse rate of >10 beats per minute during or within 4 hours of the infusion.

9.14 Hypotension
Defined as a fall in blood pressure of >10 mm Hg during or within 4 hours of the infusion.

9.15 Skin Changes
Skin changes such as urticaria during or within 24 hours of completion of the infusion.

9.16 Serious Adverse Events - see 10.1.

9.2 Efficacy in Reversal of Coagulopathy

9.21 Correction of raised INR in patients with warfarin excess to within either the therapeutic or normal ranges, depending on the clinical objective (stated on referral form).

9.22 Correction of prolonged prothrombin time to within 4 seconds of the control in patients with liver disease/transplantation.

9.23 Reversal of thrombocytopenia, haemolysis and abnormal von Willebrand factor multimers in patients with TTP.

9.3 Viral Safety

Anti-HIV 1 + 2, anti-hepatitis B core antigen, anti-HCV and anti-HAV serology will be assessed before and six months after treatment.

10.0 DATA COLLECTION

All Case Report Forms will be provided, and should be returned to the Trial Coordinator at weekly intervals. A photocopy should be retained by participating hospitals for collection by the Trial Monitor. A summary of documentation is provided in Appendix 3. This should be completed in blue or black ink. Any errors should be crossed out with a single line and the correct value entered alongside. The change should be dated and initialled by the person making the correction. The original entry should still be legible. Snopake, Liquid Paper etc. must not be used. All forms must be dated and signed. The Case Report Forms are the 'property' of the Co-sponsors ie NBA and Octapharma.

10.1 Adverse Events

An adverse event (AE) will define `any undesirable experience occurring to a subject during a clinical trial whether or not considered related to the investigational product`. A decrease in heart rate will not be considered an adverse event unless accompanied by symptomatology, morbidity, or adverse clinical signs.

A serious adverse event means an adverse experience that is fatal, life threatening, disabling, or which results in in-patient hospitalisation or prolongation of hospitalisation. An unexpected AE is an experience not previously reported (in nature, severity, or incidence) in the current Investigator's Brochure, in the General Investigational Plan, or elsewhere.

An adverse drug reaction (ADR) is a noxious and unintended reaction which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

When any adverse event occurs in the study, it will be recorded on the Adverse Reaction Sheet included in the Case Report Forms (Form 5). If the Principal Investigator judges that there are reasonable grounds for the suspicion that the adverse event is causally related to the investigational product, it will be considered as an adverse drug reaction (ADR).

All complications will be dealt with at the study site. Patients will be cared for by experienced and competent members of the medical team with access to standard emergency life-sustaining equipment.

All adverse drug reactions, as described above, will be made known to the Principal Investigator immediately (or nominated person in his absence), who will, in turn, relate them to the Sponsors' Medical Directors within 24 hours. The Principal Investigator will, also, inform the Institutional Ethical Committee of any adverse drug reaction.

Any serious adverse event will be made known to the Sponsors' Medical Directors immediately, and to the Institutional Ethical Committee within 24 hours. If any serious adverse drug reaction occurs, no further subjects will be treated in this study until the event is reviewed by the Institutional Ethical Committee. One of the Sponsors' Medical Directors (normally the NBA Medical Director) will notify the Medicines Control Agency of such an event.

10.2 Compliance with Protocol and Deviations

The final protocol of the study will be agreed by the Clinical Investigators and the Sponsors, and will be signed in confirmation of such agreement. The protocol will be approved by the local Ethics Committee. Any variations to this protocol must be agreed in advance by the Clinical Investigators and approved by the Sponsors. The Medicines Control Agency and the local Ethical Committee will be informed of any such variations. While in normal circumstances the protocol should be adhered

to, in any emergency situation, the Clinical Investigator(s) shall exercise their clinical judgement and safeguard the patient's interests. In such cases deviations from the protocol shall not require the prior approval of the Sponsors, nor of the local Ethical Committee. Any such deviations from the protocol, along with full details of the reasons for their occurrence should be reported to the Trial Co-ordinator in writing as soon as possible. A photocopy should be retained for collection by the Trial Monitor.

11.0 DATA HANDLING AND STATISTICAL CONSIDERATIONS

Data will be handled by a database program (eg Windowbase) on a Compaq 386 computer. Statistical analysis will be performed using SPSS, evaluating the data with regard to clinical tolerance of SDFFP at both low dosage (groups A and B) and high dosage (group C), and efficacy in correcting the coagulopathy of Warfarin or liver disease.

Comparisons of clinical effects and coagulation factor assays will be performed by 2-tailed non-parametric methods. It will not be possible to perform meaningful statistical comparisons of viral safety between the 2 groups because:-

1. The risks of viral transmission in the control group is already extremely low, so that thousands of patients would have to be evaluated before any true differences between the groups could be demonstrated.

2. The 2 products are fundamentally different with regard to their viral risk in that standard FFP is a single donor product, while SD FFP will be made from a pool of >300 donations. Patients receiving SD FFP will be exposed to approximately 150-300 times as many donors as patients receiving standard FFP, but the viral load from an infected donation will be somewhat reduced by dilution, irrespective of the viral killing effect of the SD process.

12.0 SPONSORSHIP AND FINANCE

The study is co-sponsored by Octapharma and the National Blood Authority.

The salary of a data collector and funding of laboratory testing, form production and computing will be financed by Octapharma.

13.0 PUBLICATION

Material intended for publication or presentation at scientific meetings will be presented to Octapharma 30 days prior to submission for publication, and published under the joint authorship of the study group.

14.0 ETHICAL CONSIDERATIONS

The study will be conducted according to the principles embodied in the EEC Guidelines for 'Good Clinical Practice for Trials on Medicinal Products'[16] and the `Declaration of Helsinki` and will be approved by the local Ethical Committee of each hospital prior to commencement. The study will involve hospital patients but no healthy volunteer subjects. Each eligible patient will receive verbal and written information from a physician about the study, and will sign an informed consent form. Permission for HIV testing will be requested separately; patients who refuse will be entered and evaluated for all other aspects of the study but will **NOT** have anti-HIV 1 + 2 testing performed. Where next-of-kin have consented to entry to the study, HIV testing will not be requested.

15.0 ADMINISTRATION

15.1 Liability

No patient will be entered into the study in any trial centre until the Principal Investigator receives a Letter of Indemnity from Octapharma giving details of the indemnity offered against claims arising from the loss or damage to patients due to their participation in the study. This must conform to ABPI Guidelines. Association of British Pharmaceutical Industries.

15.2 Licensing Arrangements

The study will be conducted under the Clinical Trial Exemption (CTX) arrangements of the Medicines Control Agency and approval of the trial will be required before any patient can be entered.

15.3 Pre-study Documentation

No trial material will be released to participating Centres by BPL until the following have been received by the Trial Monitor, Miss Sue Bhadare.

i) CTX approval.
ii) Letter of Liability from the sponsor.
iii) Copies of letters of approval from the Ethical Committee in each participating Centre.
iv) Curriculum vitae of the participants named on pages 2 and 3 of the Protocol.
v) A copy of the normal range of laboratory tests required by the Protocol from each participating Centre.
vi) A specimen copy of the patient information sheet and informed consent form to be used at each Centre, or written confirmation that the example provided with the protocol will be used (see Appendix 1).

15.4 Monitoring Responsibility

Monitoring of the trial to GCP standard will be the responsibility of Miss Sue Bhadare, who will visit each study centre at least once during the first 2 months of the 6 month study period to ensure that any misunderstandings are cleared up quickly.

15.5 Early Cessation of the Study

The Trial Sponsors and Clinical Investigators reserve the right to stop the trial if:

i) Recruitment is too slow to allow accrual of an adequate number of patients in a reasonable length of time.
ii) Evidence is gained that patients are being exposed to an unacceptable risk.
iii) For any reason, it is not possible to continue to produce the trial material.
iv) Advances in therapy make the protocol obsolete.

15.6 Maintenance of Patient's Records

The patient records should be retained for at least fifteen years and shall be made available for inspection by the Clinical Investigators and Sponsors, or by Regulatory Authorities should this be required.

16.0 REFERENCES

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15. Blumberg N and Heal JM (1988) Evidence for plasma-mediated immunomodulation-transfusions of plasma-rich blood. Components are associated with a greater risk of acquired immunodeficiency. Transplantation Proceedings, 206, 1138-1142.

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SOLVENT DETERGENT FFP STUDY APPENDIX 1

CLINICAL EVALUATION OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA, AND IN CORRECTION OF COAGULOPATHY DUE TO EITHER WARFARIN OR LIVER DISEASE

Your doctor has decided that as part of your treatment, you require 1 or more infusions of plasma. The plasma you will receive is made from voluntary blood donations and is tested for the presence of the viruses which cause AIDS and hepatitis.

This means that the plasma which is currently available is extremely safe with regard to infection. However, a new method of treating plasma has been developed to make it even safer by killing the bulk of any viruses which may be present.

We are inviting you to take part in a study comparing the new treated plasma with our standard plasma, by agreeing to be allocated to receive either standard or treated plasma. Other studies of the new plasma are also taking place in other parts of the world, but this would be the first formal assessment in the UK. This assessment involves giving some patients standard plasma, and some patients the new product, on a random basis, and would enable this new plasma to eventually become generally available for all patients. To prevent bias, you will not know which plasma you have received until all assessment has been completed.

The method used to treat the plasma has been used on other blood products for the past 6 years, without any short-term or long-term side-effects. Taking part in the study will not interfere with any other treatment you may be receiving. If you agree to take part, we will require 1 or 2 extra blood samples to check your blood clotting, and to prove that there is no evidence of infection with viruses which may cause hepatitis or AIDS (the HIV virus). We will also have to contact you in 6 months' time for a final blood sample.

IF YOU ARE NOT HAPPY TO HAVE YOUR BLOOD TESTED FOR THE AIDS VIRUS, YOU ARE UNDER NO PRESSURE TO DO SO. YOU CAN STILL TAKE PART IN THE STUDY AND HAVE THE OTHER SAMPLES TAKEN. WE WILL NOT TEST YOUR BLOOD FOR THE AIDS VIRUS WITHOUT YOUR WRITTEN PERMISSION.

You will be free to withdraw from the study at any time without having to explain why. All information collected will be kept confidential. Any abnormal results will be communicated to you. However, if you are agreeable, we will tell your GP that you have been in the study. If you have any questions about the study, please ask Dr _____.

CONSENT BY PATIENT OR VOLUNTEER TO PARTICIPATION IN CLINICAL TRIAL OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA

I, ...

of .....

hereby fully and freely consent to participate in the controlled clinical trial entitled:

CLINICAL EVALUATION OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA, AND IN CORRECTION OF COAGULOPATHY DUE TO EITHER WARFARIN OR LIVER DISEASE

I understand and acknowledge that the trial is designed to add to medical knowledge. I note that I may withdraw my consent at any stage in the investigation and I understand that full legal indemnity is provided by the manufacturer. I acknowledge that the purpose of the trial, the risks involved from drugs or other procedures, and the nature and purpose of such procedures have been explained to me by:

..... and that I had an opportunity to discuss these matters with him/her.

I have received a written explanation of these matters, a copy of which is attached to this form.

Signed .....
WITNESS to signature of patient/volunteer and to fact that he/she has read the document and freely given his/her consent.

Signed .....
(Witness must not be a member of project team)

I confirm that I have explained to the patient/volunteer the nature and effect of these procedures.

Signed .....
(Member of project team acting on behalf of Physician/Surgeon responsible for investigation)

Date .....Place .....

CONSENT FOR HIV TESTING

I ..... of .....

hereby fully and freely consent to having my blood tested for antibody to HIV (the AIDS virus) as part of a research trial.

I understand that the result will be communicated to me if it is abnormal, but not to other individuals without my written permission.

The test has been explained to me by Dr ....., and I have had the opportunity to discuss the test with him/her.

Signed .....

Witness

I confirm that I have explained the nature of the HIV test to the patient.

Signed .....

YOUR BLOOD WILL NOT BE TESTED FOR HIV WITHOUT YOUR WRITTEN PERMISSION

CONSENT BY NEXT OF KIN TO THE PARTICIPATION BY A PATIENT WHOSE CONDITION/ILLNESS PRECLUDES THEIR UNDERSTANDING THE NATURE OF THE INVESTIGATION IN A CLINICAL TRIAL OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA

I, ...

of .....

being the next of kin of

.....

.....

hereby give my permission fully and freely for the patient to participate in the controlled clinical trial entitled:

CLINICAL EVALUATION OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA, AND IN CORRECTION OF COAGULOPATHY DUE TO EITHER WARFARIN OR LIVER DISEASE

I note that I may withdraw my consent at any stage in the investigation and I understand that full legal indemnity is provided by the manufacturer. I acknowledge that the purpose of the trial, the risks involved from drugs or other procedures and the nature and purpose of such procedures have been explained to me by:

.....

and that I have had an opportunity to discuss these matters with him/her.

I have received a written explanation of these matters, a copy of which is attached to this form.

Signed .....

WITNESS to next of kin's signature and to the fact that he/she has read the document and freely given his/her consent.

Signed .....

(Witness must not be a member of project team)

I confirm that I have explained to the next of kin of the patient the nature and effect of these procedures.

Signed .....

(Member of project team acting on behalf of Physician/Surgeon responsible for investigation)

Date ..... Place .....

DATE: .....

Researchers' Names (contact name first) address and telephone number)

Dr. Lorna Williamson
Division of Transfusion Medicine,
University of Cambridge,
Long Road,
Cambridge.
CB2 2PT

Telephone: Cambridge GRO-C Fax: GRO-C

To: Dr. .....

Dear Doctor

The person named below, who is registered with you, took part in our research project as a patient and has consented to our contacting you. The project was approved by the Ethical Committee. We are writing to inform you that certain abnormal findings or possible adverse effects of the research were noted.

Please keep this as a permanent record of your patients' involvement.

Name of subject	Date of birth	Date(s) of study
.....	d m y	.....

Title of Project:

CLINICAL EVALUATION OF SOLVENT-DETERGENT TREATED FRESH FROZEN PLASMA IN THE MANAGEMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA, AND IN CORRECTION OF COAGULOPATHY DUE TO EITHER WARFARIN OR LIVER DISEASE

Details of treatment given:

.....

.....

Details of abnormal findings or possible adverse effects:

.....

.....

Action taken:

.....

.....

.....

SOLVENT DETERGENT FFP STUDY APPENDIX 2

SUMMARY OF RANDOMISATION, DOCUMENTATION AND SAMPLING

Eligibility

- Adult patients (> 18 years) of groups O or A who need FFP for:-
  - Warfarin reversal
  - liver disease
  - liver transplant
  - newly diagnosed TTP

Exclusions

- Age < 18 years.
- Blood group B or AB.
- Pregnancy
- Previous reactions to FFP.
- Blood products within previous six months (Warfarin/liver disease patients only).
- Rh negative with anti-D.

Warfarin, Liver disease, Liver transplant → Randomise → Standard FFP → Follow up for 24 hours
Randomise → SD FFP → Follow up for 24 hours

TTP → SD FFP → Daily follow-up till treatment completed (up to 14 days)

1. Obtain informed patient consent and signature.
2. Open randomisation envelope for allocation and trial number. Be sure to randomise in correct diagnostic group.
3. Fill in registration form (Form 1), and take pre-treatment citrated and clotted samples. Fill in pre-treatment information form (Form 2a, b, or c) once results of sample investigation e.g. PTT/INR are available.
4. Record all FFP infusions on treatment record (Form 3) and clinical parameters on observation card (Form 4). Take citrated samples 30 minutes and 24 hours from the end of the infusion. (TTP patients see Appendix 3b.)
5. Record all adverse events on Form 5, and telephone/fax Study Co-ordinator within 24 hours.
6. At completion of treatment, or withdrawal, complete post-treatment information form (Form 6) once 30 minutes and 24-hour PTT/INR results available.

---

10 mls CITRATED PLASMA
(separated and frozen)
Label SD FFP + Trial number and time and date
(Pre, 30 minutes, 24 hours etc.)

10 mls CLOTTED SAMPLE
Whole Blood
Label SD FFP + Trial number and date
(Pre or 6 months post)

→ Coagulation Laboratory (SD FFP Study)
Haematology Department,
Addenbrooke's Hospital,
Cambridge.

→ Virology Laboratory (SD FFP Study),
East Anglian Blood Transfusion Centre,
Long Road, Cambridge

Address stickers provided

CLINICAL AND LABORATORY EVALUATION - WARFARIN AND LIVER DISEASE/TRANSPLANT GROUPS

CLINICAL MONITORING

(times are from beginning of infusion)

	Pretreatment	15 minutes (Liver transplants only)	30 minutes	1 hour	2 hours	4 hours	24 hours (not liver transplants)
Pulse	X	X	X	X	X	X	
Temperature	X	X	X	X	X	X	
Blood pressure	X	X	X	X	X	X	
Skin examination	X	X	X	X	X	X	X

LABORATORY PARAMETERS * = Liver transplants only	Pretreatment	30 minutes post completion of infusion	24 hours post completion of infusion	6 months
PT/INR	X	X		
PTTK	X	X		
Fibrinogen*	X	X	X	
Factor II	X	X	X	
Factor V*	X	X	X	
Factor VII*	X	X	X	
Factor VIII*	X	X	X	
Protein C	X	X	X	
Anti-HCV	X			X
Anti-HIV 1 + 2	X			X
Anti-Hep B core Antigen	X			X
Anti-HAV	X			X

SOLVENT DETERGENT FFP STUDY

APPENDIX 3B

CLINICAL AND LABORATORY EVALUATION - TTP PATIENTS

CLINICAL MONITORING

(times are from beginning of infusion

	Pretreatment	15 minutes	30 minutes	1 hour	2 hours	4 hours	24 hours
Pulse	X	X	X	X	X	X	
Temperature	X	X	X	X	X	X	
Blood pressure	X	X	X	X	X	X	
Skin examination	X	X	X	X	X	X	X

LABORATORY PARAMETERS (samples should be taken each day prior to commencement of plasma infusion/exchange)

	Pretreatment Day 1	Day 2	Day 3	Day 4	Daily	24 hours after last plasma	6 months after last plasma infusion /exchange
Hb	X	X	X	X	X	X	
WCC	X	X	X	X	X	X	
Platelets	X	X	X	X	X	X	
Blood film	X	X	X	X	X	X	
PT (secs)	X	X	X	X	X	X	
PTTK/KCCT (secs)	X	X	X	X	X	X	
vWf multimers	X	X	X	X	X	X	
Creatinine	X	X	X	X	X	X	
LDH	X	X	X	X	X	X	
Anti-HCV	X						X
Anti-HIV 1 + 2	X						X
Anti-Hep B core Antigen	X						X
Anti-HAV	X						X

SOLVENT DETERGENT FFP STUDY REGISTRATION FORM

Please complete and return to Trial Coordinator:

Dr. Lorna Williamson,
Division of Transfusion Medicine,
University of Cambridge,
Long Road, Cambridge CB2 2PT

Patient's full name and address:		Date of birth: day / month / year Ethnic origin:
Name and address of patient's G.P.		
Hospital name and full address:		
Hospital number:	Consultant:	
Trial number:	Allocation:	Date of registration: day / month / year

CHECKLIST FOR ENTRY

INCLUSION

Patient entered because:		Tick		
1.	Warfarin excess requiring urgent reversal		☐	
2.	Prolonged prothrombin time due to liver disease		☐	
3.	Prolonged prothrombin time prior to liver transplantation		☐	
4.	TTP		☐	
5.	Patient is group O or A	Yes	☐	No ☐
		O ☐ A ☐		
6.	Patient is over 18 years		☐	☐

At least one of the above should be ticked and ***YES*** to other to be included.

EXCLUSION

·	Patient is <18 years	Yes	☐	No ☐
·	Patient is either blood group B or AB	Yes	☐	No ☐
·	Patient is pregnant	Yes	☐	No ☐
·	Patient has previous reactions to FFP	Yes	☐	No ☐
·	Patient has had blood products within previous 6 months (Warfarin and liver disease patients only)	Yes	☐	No ☐
·	Patient is Rhesus negative with anti-D	Yes	☐	No ☐

If there are any **YES** responses in this section, this patient is not eligible.

SOLVENT DETERGENT FFP STUDY — FORM 1
ALL PATIENT GROUPS: REGISTRATION

Patient's Initials: [| |]

Date of registration: [d | m | y]

Patient's date of birth: [d | m | y]

Sex: [Male | Female]

Tick [|]

Name and address of patient's GP:

Hospital name and address:

Hospital number:

Consultant:

For entry because:- Tick

1. Warfarin excess requiring urgent reversal [ ]
2. Prolonged prothrombin time due to liver disease [ ]
3. Prolonged prothrombin time prior to liver transplantation [ ]
4. TTP [ ]

Please open randomisation envelope.

<u>Be sure you are randomising in the correct diagnostic group</u>

Blood group (please tick)

[A] [O]

Trial number: [ ]

Allocation: Standard FFP [ ] SD FFP [ ]

Initial samples taken (date and time):
(See Protocol for samples required)

[d | m | y]

[Hr | Min]
24 hours

Comments: Blood products in preceding 6 months?
(TTP and liver transplantation groups only)
Give details (products and dates) if possible

[Yes] [ ] [No] [ ]

If yes, which products .....
.....
..... and date(s) [d | m | y]

Has patient or next of kin signed consent form? [Yes] [ ] [No] [ ]

Has permission for HIV testing been obtained? [Yes] [ ] [No] [ ]
(Not to be sought from next of kin)

Form completed by: (signature) _____ Date: [d | m | y]

SOLVENT DETERGENT FFP STUDY — FORM 2a

WARFARIN REVERSAL: PRE-TREATMENT INFORMATION

Patient's initials:	Patient's date of birth: d m y	Trial number:

Hospital: | Consultant:

Diagnosis and reason for Warfarin therapy:

Duration of Warfarin therapy:
- <2 weeks [ ]
- 2-8 weeks [ ]
- >8 weeks [ ]

Reason for Warfarin reversal (give brief details):

Are you aiming to return the INR to:
- therapeutic range [ ]
- normal [ ]

Signs of haemorrhage: Yes [ ] No [ ]

If yes, from where?:

Concomitant medication:
Give dosage and duration

Patient's weight (kg)

WILL YOU GIVE VITAMIN K ALSO?: Yes [ ] No [ ]
Give dosage and route:

If yes, this should be given 30 minutes after the FFP.

PRE-TREATMENT:

INR _____ PTTK/KCCT (secs) _____

Control (secs) _____

Form completed by: (signature) _____ Date: d m y

For Laboratory Use Only:

Fibrinogen	g/l	_____	Anti-HIV 1 + 2	_____
Factor II	u/dl	_____	Anti-Hep B core Ag	_____
Factor VII	u/dl	_____	Anti-HCV	_____
Protein C	u/dl	_____	Anti-HAV	_____

SOLVENT DETERGENT FFP STUDY: FORM 2b

LIVER DISEASE: PRE-TREATMENT INFORMATION

Patient's initials:	Patient's date of birth: d m y	Trial number:

Hospital:	Consultant:

Diagnosis and reason for FFP administration?

Signs of haemorrhage: Yes ☐ No ☐

If yes, from where?:

Concomitant medication: Give dosage and duration	Patient's weight (kg)

PRE-TREATMENT:

Prothrombin time (seconds) Pt _____ Control _____ PTTK/KCCT (secs)_____

ISI of thromboplastin used _____ Control _____

Form completed by: (signature) _____ Date: d m y

For Laboratory Use Only:

Fibrinogen	(g/l)	_____	Anti-HIV 1 + 2		_____
Factor II	(u/dl)	_____	Anti-Hep B core Ag		_____
Factor VII	(u/dl)	_____	Anti-HCV		_____
Protein C	(u/dl)	_____	Anti-HAV		_____

SOLVENT DETERGENT FFP STUDY: FORM 2c

LIVER TRANSPLANTATION: PRE-TREATMENT INFORMATION

Patient's initials:	Patient's date of birth: ⌜ ⌝ ⌜ ⌝ ⌜ ⌝ d m y	Trial number:

Hospital:	Consultant:

Diagnosis and reason for FFP administration?

Signs of haemorrhage: Yes ⌜ ⌝ ⌞ ⌟ No ⌜ ⌝ ⌞ ⌟

If yes, from where?:

Concomitant medication: Give dosage and duration	Patient's weight (kg)

PRE-TREATMENT:

Prothrombin time (seconds) Pt _____ Control _____ PTTK/KCCT (secs) _____

ISI of thromboplastin used _____ Control _____

Form completed by: (signature) _____ Date: ⌜ ⌝ ⌜ ⌝ ⌜ ⌝ d m y

For Laboratory Use Only:

Fibrinogen	(g/l)	_____	Anti-HIV 1 + 2	_____
Factor II	(u/dl)	_____	Anti-Hep B core Ag	_____
Factor V	(u/dl)	_____	Anti-HCV	_____
Factor VII	(u/dl)	_____	Anti-HAV	_____
Factor VIII	(u/dl)	_____		
Protein C	(u/dl)	_____		

SOLVENT DETERGENT FFP STUDY: TTP : PRE-TREATMENT INFORMATION

FORM 2d

Patient's initials:	Patient's date of birth: d m y	Trial number:

Hospital: | Consultant:

Diagnostic features:

Signs of haemorrhage: Yes ☐ No ☐

If yes, from where?:

Concomitant medication:
Give dosage and duration

Patient's weight (kg)

Previously transfused with:

Red cells:	Yes ☐	No ☐
FFP:	Yes ☐	No ☐
Platelets:	Yes ☐	No ☐
If so, any febrile reactions?:	Yes ☐	No ☐
Renal impairment:	Yes ☐	No ☐
Neurological manifestations?:	Yes ☐	No ☐

PRE-TREATMENT:

Prothrombin time (secs)	Pt _____ Control _____	ISI of thromboplastin	_____
PTTK (secs)	Pt _____ Control _____	Plt count (x 10^9/l)	_____
Hb (g/dl)	_____	LDH units/l	_____
Plt count (x 10^9/l)	_____	LDH units/l	_____
Creatinine umol/l	_____		

Blood film - Red cell fragmentation Yes ☐ No ☐

Form completed by: (signature) _____ Date: d m y

For Laboratory Use Only:

Anti-HIV 1 + 2	_____	Anti-HCV	_____
Anti-Hep B core Ag	_____	Anti-HAV	_____

Von Willebrand Factor Multimers Normal ☐ Abnormal ☐

If abnormal, give details:

SOLVENT DETERGENT FFP STUDY: FORM 3

ALL PATIENT GROUPS : TREATMENT RECORD

Patient's initials:	Patient's date of birth: d m y	Trial number:	Sheet number:

Receiving: Standard FFP ⌜ ⌝ ⌞ ⌟ SD FFP ⌜ ⌝ ⌞ ⌟

Date	Time infusion started	Number and volume of units	Donation numbers OR Batch numbers	Other blood products given within 24 hours			Drugs within 24 hours		
d m y	24 hours			Type	Amount (l)	Time 24 hrs	Name	Dose /Route	Time 24 hrs

Form completed by: (signature) _____ Date: d m y

SOLVENT DETERGENT FFP STUDY: FORM 4

ALL PATIENT GROUPS: OBSERVATION RECORD

(Use 1 sheet for each day's treatment)

Patient's initials:	Patient's date of birth: d m y	Trial number:	Sheet number:
Receiving:	Standard FFP ⌜ ⌝ ⌞ ⌟	SD FFP ⌜ ⌝ ⌞ ⌟	
Date: d m y	Time Treatment Started (24 hours)	Time Treatment Completed (24 hours)	

	Pulse b/min	Temperature °C	Blood Pressure mm/hg	Skin changes Yes / No (Mild/Moderate/Severe)
Pre-treatment				
15 *minutes from start of infusion* (Liver transplants and TTP only)				
30 *minutes from start of infusion*				
1 hour from start of infusion				
2 hours from start of infusion				
4 hours from start of infusion				
24 hours from start of infusion (Not liver transplants)				

FOR TTP PATIENTS ONLY:-

Is plasma exchange being performed today?

If so, how many litres? ____

Form completed by: (signature) _____ Date: d m y

SOLVENT DETERGENT FFP STUDY: FORM 5

ALL PATIENT GROUPS: ADVERSE EVENTS

This form should be used to report all adverse events occurring within 24 hours of infusion of FFP/SDFFP, whether or not they are thought to be related to treatment

Has an adverse event occurred? Yes ☐ No ☐

Patient's initials:	Patient Number:	Trial Number:	Date of observation:
☐☐☐	☐☐☐☐☐	☐☐☐☐☐	☐☐ d ☐☐ m ☐☐ y

Patient received: Standard FFP ☐ SD FFP ☐

Patient group:

Warfarin reversal: ☐ Liver Disease: ☐ Liver Transplant: ☐ TTP ☐

Severity: Mild ☐ Moderate ☐ Severe ☐

Description of adverse event:.....

.....

Duration of adverse event:

Start ☐☐ d ☐☐ m ☐☐ y Stopped ☐☐ d ☐☐ m ☐☐ y Ongoing ☐

Time ☐☐☐ (24 hours) Time ☐☐☐ (24 hours)

Relationship to investigational treatment:

Probably ☐ Possibly ☐ Unlikely ☐ Not Assessable ☐

Management of investigational treatment:

Continued same dosage ☐ Permanently stopped treatment ☐

Decreased dosage ☐ End of trial ☐

Temporarily stopped treatment ☐

Other treatment given (please give details).....

.....

Outcome

Patient recovered ☐ Symptoms persisted ☐ Other ☐

If `persisted` or `other` please give details .....

.....

IF THE ADVERSE EVENT IS SEVERE OR A DEATH OCCURS, IT MUST BE REPORTED IMMEDIATELY TO

THE TRIAL COORDINATOR: *Dr. Lorna Williamson Telephone: 0223 245921/Fax: 0223 411618*

or PRINCIPAL INVESTIGATOR: *Dr. F. Ala Telephone: 021 4141155/Fax: 021 4141308*

SOLVENT DETERGENT FFP STUDY: FORM 6a

WARFARIN REVERSAL: POST TREATMENT INFORMATION

Patient's initials:	Patient's date of birth: d m y	Trial number:
Hospital:		Consultant:

30 minutes from end of infusion:	24 hours from end of infusion:
Samples taken -	Samples taken -
Date: d m y	Date: d m y
Time: _____ 24 hours	Time: _____ 24 hours
RESULTS	
30 minutes	24 hours
INR	**INR**
PTTK/KCCT (secs)	PTTK/KCCT (secs)
Control (secs)	Control (secs)
Form completed by: _____	Date: d m y

Amount of Vitamin K administered if any:-

For Laboratory Use Only

		30 minutes			24 hours
Fibrinogen	(g/l)	_____	Fibrinogen	(g/l)	_____
Factor II	(units/l)	_____	Factor II	(units/l)	_____
Factor VII	(Units/l)	_____	Factor VII	(units/l)	_____
Protein C	(units/l)	_____	Protein C	(units/l)	_____

Six months after infusion:

Samples taken - Date: d m y

Anti-HCV _____

Anti-HIV 1 + 2 _____

Anti-Hep B core Ag _____

Anti-HAV _____

SOLVENT DETERGENT FFP STUDY: FORM 6b

LIVER DISEASE: POST TREATMENT INFORMATION

Patient's initials:	Patient's date of birth: d m y	Trial number:
Hospital:	Consultant:	

30 minutes from end of infusion:

Samples taken -

Date: d m y

Time: _____ 24 hours

24 hours from end of infusion:

Samples taken -

Date: d m y

Time: _____ 24 hours

RESULTS

	30 minutes	24 hours
Prothrombin time (secs)	Patient ___ Control ___	Patient ___ Control ___
PTTK/KCCT (secs)	Patient ___ Control ___	Patient ___ Control ___

Form completed by: _____

Date: d m y

For Laboratory Use Only

		30 minutes	24 hours
Fibrinogen	(g/l)	_____	_____
Factor II	(units/l)	_____	(unit/l) _____
Factor VII	(units/l)	_____	(unit/l) _____
Protein C	(units/l)	_____	(unit/l) _____

Six months after infusion:

Samples taken - Date: d m y

Anti-HCV _____

Anti-HIV 1 + 2 _____

Anti-Hep B core Ag _____

Anti-HAV _____

SOLVENT DETERGENT FFP STUDY: FORM 6c

LIVER TRANSPLANTATION: POST TREATMENT INFORMATION

Patient's initials:	Patient's date of birth: (d m y)	Trial number:

Hospital:	Consultant:

30 minutes from end of infusion:	24 hours from end of infusion:
Samples taken -	Samples taken -
Date: (d m y)	Date: (d m y)
Time: _____ 24 hours	Time: _____ 24 hours

RESULTS	
30 minutes	24 hours
Prothrombin time (secs) Patient ——— Control ———	Prothrombin time (secs) Patient ——— Control ———

Form completed by: _____	Date: (d m y)

For Laboratory Use Only

		30 minutes			24 hours
Fibrinogen	(g/l)	_____	Fibrinogen	(g/l)	_____
Factor II	(units/l)	_____	Factor II	(units/l	_____
Factor V	(units/l)	_____	Factor V	(units/l)	_____
Factor VII	(units/l)	_____	Factor VII	(unilt/l)	_____
Factor VIII	(units/l)	_____	Factor VIII	(units/l)	_____
Protein C	(units/l)	_____	Protein C	(units/l)	_____

Six months after infusion:

Samples taken - Date: (d m y)

Anti-HCV	_____
Anti-HIV 1 + 2	_____
Anti-Hep B core Ag	_____
Anti-HAV	_____

SOLVENT DETERGENT FFP STUDY: TTP : POST TREATMENT INFORMATION

FORM 6d

Patient's initials:	Patient's date of birth: (d m y)	Trial number:
Hospital:	Consultant:	

Day of treatment d m y	Hb (g/dl)	Platelet count (x 10^9/l)	Red cell fragmentation in film yes / no	WCC x10^9/l	Creatinine µmol/l	LDH units/l	PT (secs) *Patient and control*	PTTK/KCCT (secs) *Patient and control*	vWf factor multimer yes / no
1							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
2							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
3							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
4							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
5							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
6							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
7							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
8							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
9							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
10							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
11							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
12							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
13							Pt _____ Ctrl _____	Pt _____ Ctrl _____	
14							Pt _____ Ctrl _____	Pt _____ Ctrl _____	

Form completed by: (signature) _____ Date: (d m y)

For Laboratory Use Only

At six months:-

Date taken: (d m y)

Anti-HCV_____ Anti-HIV 1 + 2 _____ Anti-Hep B core Ag _____ Anti-HAV _____

Comments on clinical outcome: