Special Meeting of the Scottish and
Northern Ireland Factor VIII Working Party
held in Seminar Room, Haemophilia Centre,
Royal Infirmary 9 November 1988

Present:

Dr C A Ludlam, Chairman, Royal Infirmary, Edinburgh
Dr G D O Lowe, Royal Infirmary, Glasgow
Dr B E S Gibson, Royal Hospital for Sick Children, Glasgow
Dr E Mayne, Royal Victoria Hospital, Belfast
Dr P Foster, Protein Fractionation Centre, Edinburgh
Dr B Cuthbertson, Protein Fractionation Centre, Edinburgh
Dr R Stewart, SNBTS HQ Unit, Edinburgh
Dr R J Perry, Protein Fractionation Centre, Items

1. INTRODUCTION AND APOLOGIES FOR ABSENCE

Dr Ludlam welcomed the members to the meeting. Apologies were received from Professor Cash and Dr McClelland.

2. MINUTES OF PREVIOUS MEETING

Minutes of the meeting dated 6 October 1988 were read and they were agreed to represent a true record of the meeting.

3. FUTURE MEETINGS

The regular meeting of the Working Party scheduled for 17 November 1988 has been cancelled. The next meeting will take place on 12 December 1988 starting at 10.30am in the Seminar Room, Haemophilia Centre (Room 45), Royal Infirmary, Edinburgh.

4. FUTURE DEVELOPMENTS OF FACTOR VIII PRODUCTS BY PFC

Dr Ludlam introduced the discussion by presenting a profile of an ideal Factor VIII product forseen over the next 1-5 years. He also highlighted some of the problems encountered with the current product. These were:

a. Is the FVIII c content not as active in vivo as in vitro?
b. Is the current Factor VIII product as effective in von Willebrand's disease as previous Factor VIII products?
c. The unitage per vial is variable.
d. The product is slow to go to solution
e. The product is of low purity
f. The product leads to immune modulation
g. Allergic reactions occur
h. As with any blood product there remains a potential of transmission of viruses particularly hepatitis B, delta agent, NANB hepatitis and, less likely, HIV

Dr Lowe commented that due to the lack of effect of the Factor VIII concentrate in von Willebrand's disease they tended to cover operations of such patients with cryoprecipitate. Dr Mayne commented that even when the correct dose of Factor VIII concentrate is given and elevated plasma factor VIII levels are achieved, some patients haemohilia A report little improvement. She commented that a higher dose of factor VIII concentrate is needed. All the Haemophilia Directors agreed they had patients who had made similar comments.

Dr Cuthbertson said that PFC was working on solubility and said that this problem had been predicted when heat treatment was increased to 80C. The new product (son of Z8) will dissolve mo[illegible] quickly. Dr Foster then presented the plan for development of Factor VIII in PFC. He commented that due to the shape of the curve of plamsa required to maintain output as yield falls (see appendix 1), it would be difficult to adopt a process which would yield less than 200 international units per litre. He also commented that due to the report of the Medicines Inspectorate it was not possible currently for PFC to take any more plasma for fractionation.

Dr Ludlam asked what was the absolute ceiling of plasma that PFC could process. Neither Dr Foster nor Dr Cuthbertson felt that they could answer this and the question was referred to Dr Perry when he attended later. Dr Foster then reviewed the process options available. Dr Ludlam commented that the solvent detergent treatment was potentially the most interesting virucidal step and enquired what was the likely yield penalty. Dr Foster reported that this would be in the region of 10-40 per cent which is comparable to the report yield loss of 25% due to dry heat. However Dr Cuthbertson pointed out that t[illegible] introduction of solvent detergent treatment would be in addition to final dry heat treatment and therefore losses would have to be sumed.

Dr Ludlam also pointed out that there are little data available on the long term effects of traces of solvent and detergent left in blood products infused to patients. He requested Dr Foster to collate what data there were on the toxicity of traces of solvent-detergent left as these were potent membrane distrupters.

Dr Foster pointed out that dry heating of Factor VIII had been introduced to inactivate HIV, and activity against the NANBH agent had not been a primary objective. The effectiveness of this treatment depends on several factors. These are: the freeze drying process, final moisture content, formulation, stabilisers and crystal structure of the powder. Good control of the moisture content was now achieved and Dr Foster reported that PFC had gained at lot of extra expertise on freeze drying in the last 2 years. The mean moisture content of vials entering the dry heat treatment process is 1% with a range of 0.2%. Dr Cuthbertson pointed out that below 0.5% water content there is markedly reduced virus kill and above 2% moisture content there are solubility and yield penalties. Dr Foster commented that

they had achieved a consistent crystal structure by supercooling the liquid to -5C, and then inducing quick freezing. Dr Lowe then enquired whether every future batch of Factor VIII will be treated at 80C rather than 75C as the safety data published on the use of 8Y referred to 80C treatment. Dr Foster reported that the 75C batches had been necessitated because a breakdown had occurred in a special cold room which had lead to a product which had a lower Factor VIII content and an increased fibrinogen content. Previous experience had led the production group at PFC to predict that 80C treating of this batch would lead to severe problems. A new cooling unit has been installed so it was anticipated that 80C treatment would be available for all new batches in future. Additionally knowledge has been gained on how to perform the specific cooling techniques manually, so that if there are any future problems in the cold room, production can continue. Dr Foster also pointed out that with the son of Z8 this should not be such a problem.

Dr Lowe enquired about the efficacy of various temperatures in killing viruses. Dr Cuthbertson presented data which showed four logs of inactivation of HIV by treatment at 68C for 24 hours, but only 0.6 log of Vacinnia (a more heat stable virus). Increasing the treatment to 75C for 72 hours increased the kill of Semliki Forrest Virus (a Togavirus, possibly similar to the Non-A Non-B hepatitis agent) but only doubled the kill of Vaccinia. Increasing the temperature from 75 to 80C once more doubled the kill of Vaccinia. HSV lost 5 logs of activity over 68C for 24 hours. Polio virus is inactivated by the freeze-drying cycle. 4 logs of mumps virus are inactivated by 68C for 24 hours.

Dr Foster commented that there is a UK Working Party (consisting of members of Blood Transfusion Services and National Institute for Biological Standards and Control) which is looking at requirements to demonstrate viral inactivation in blood products. Dr Cuthbertson emphasised that the main point of the PFC paper was to demonstrate that dry heat treatment is an effective virucidal step but that each process is unique and any changes to the process need to be validated individually.

Dr Cuthbertson suggested that at 80C an event occurs which inactivates the Non-A Non-B hepatitis agent. Dr Ludlam enquired what would happen if there was an equipment failure and it was not possible to produce 80C treated product for a short period. Dr Stewart pointed out there was a strategic objective to develop a 3 month stock of Factor VIII in the Scottish Health Service which should hopefully avoid such a crisis. Dr Foster commented such a position may require a decision to be made by the Haemophilia Directors whether they would prefer to have a poorly soluble product or one which was treated at 75C.

Dr Ludlam enquired what was the current national stock of Factor VIII. Dr Cuthbertson said that he believed this to be in the region of 1 million of which about 400,000 international units were held in PFC and about 600,000 held in Regional Transfusion Centres.

It was agreed that the hepatitis B remains a problem and that the inactivation of the hepatitis B virus requires to be demonstrated. The potential of hepatitis B transmission by SNBTS Factor VIII products was discussed. The Royal Infirmary of Edinburgh received a 75C treated Factor VIII which was given to 2 patients.

The Royal Hospital for Sick Children had one patient who had developed hepatitis B, though Dr Cuthbertson pointed out that the data on this patient were incomplete as he had received several different factor VIII products, including NY. A single patient in Glasgow is known to be infected with the hepatitis delta agent which was transmitted by a non-SNBTS factor VIII product whil this patient was under treatment in Northern Ireland. It was agreed that there is no cases of hepatitis B unequivocably associated with 80C treated factor VIII concentrates.

Dr Ludlam then requested members of the working party to produce a consensus on viral inactivation processes. Dr Ludlam agreed that he would enquire what were the current FDA virucidal inactivation requirements.

Dr Lowe commented while the solvent-detergent treatment was attractive he was concerned about the long term risk of traces of solvents entering patients' body fats. He commented that it was difficult to get a good estimate of the risk of individual products far less compare different products. He also commented that the Mannucci paper showed that the efficacy of many of the viral activation processes were similiar. Additionally it is necessary to study many batches as well as many patients with a single batch.

Dr Mayne commented that while there was a lot of international discussion on the solvent-detergent treatment she felt that when considering all the data, and this was only done in specialised groups such as this, she was not convinced that any single treatment could be considered a gold standard and she believed that current evidence suggested that final vial dry heat treatment was as good as any other. She expressed concern about long term effects of solvent-detergent exposure to patients and said it was difficult to get the proper toxicity studies done as this would require evidence on up to 15 year patient exposure, before we know how solvent-detergent traces can effect our patients. Also with products such as Monoclate she was concerned about continual exposure to mouse proteins.

Dr Gibson commented that while she came to the meeting with a bias in favour of solvent-detergent treatment she was now moving closer to favouring dry heat treatment.

Dr Stewart commented that in his opinion the strength of dry heat treatment remained that it was a final product treatment and that there was no risk of recontaminating the product after the virucidal step. In a relatively small producer like PFC, where manufacturing equipment or even areas may have to be shared between different products this was of paramount importance.

Dr Foster pointed out that dry heating was not a fixed process and will continue to evolve, but that PFC was committed to a terminal process. If any other virucidal process was introduced it will be in addition to final processing and that such changes cannot be taken on lightly as they would take 2-3 years to validate. Dr Cuthbertson pointed out that since PFC was now intending to licence all its products and applications were taking 18 months to be processed by the DHSS, developments must be planned.

Dr Ludlam enquired whether the higher purity factor VIII product to be produced by PFC will also be treated at 80C. Dr Foster commented that formulation has such an effect on the virucidal action of heat treatment that it is not inconceivable that treatment at 50C of a higher purity product may be more virucidal than 80C treatment of the current product. There remains the need to do model virus studies on each process alteration but the commitment to terminal treatment will remain.

Dr Lowe enquired whether factor IX is to be 80C treated and expressed concern about hypercoagulability associated with this product. Dr Foster informed the group that PFC was developing a higher purity factor IX product which would be less thrombogenic. Animal models had been set up and were now freely available.

At this point Dr Perry joined the group.

5. IDEAL FACTOR VIII PRODUCT

Dr Ludlam requested members of the working party to suggest what they thought would be an ideal factor VIII product. Dr Mayne said she would require something which was safe and pure, available in a small volume, be efficacious, easy to make up, especially quickly soluble and have no side effects. Monoclonal products may look attractive but what is the yield cost? Additionally it is important to have a clinical assessment of the haemostatic properties of any new product.

Dr Perry pointed out that the son of Z8 will be 2-3 international units per milligram of protein.

The result a discussion on the immune disturbance of which is seen in HIV negative haemophiliacs. Dr Foster commented that 12 candidates including the underlying disease had been implicated for causing the immune disturbance. These candidates include beta 2 microglobulin, immunoglobulin G against T cell receptors, total protein overload, many fractionation reagents and transglutamidase. Dr Foster also commented that it was not

normal fractionation policy to go for increased purity per se but rather a strategy should be developed to eliminate specific identifed contaminants. We must know what it is that needs to be removed. He commented that the improved Z8 should be available next year and that the higher purity factor VIII with 50-100 international units per milligram should be available 2-3 years thereafter, and then, if considered appropriate, an extremely high purity of 500-1000 units per milligram could be available in 5 years. The new son of Z8 is considered a stepping stone towards the high purity products.

Monoclate has an activity of 15-20iu per milligram as albumin is added back as stabiliser. Genetically engineered factor VII products could have a 90% purity but also are likely to need protein stabilisation.

Dr Ludlam enquired about the time scale for development of factor VIII. In response to this enquiry, Dr Stewart produced the development schedule for new SNBTS factor VIII (see appendix 2). Dr Ludlam enquired whether we would need to do the PUP study before applying for a product licence. Dr Mayne, Dr Perry, Dr Stewart and Dr Lowe however did not think we would need to do so. Dr Stewart and Dr Perry proposed that the phase I study of the new factor VIII product be done at a professional pharmacology unit such as Drug Development (Scotland) Limited in January 1989. They also supplied a copy of a schedule with ideal requirements for phase I study (see appendix 3).

The proposal to have the phase I study done at Drug Development Scotland (DDS) was discussed extensively and Dr Mayne pointed out that she regularly reviewed such data for commercial factor VIII suppliers and that she applauded attempts to produce data of similar quality for future PFC factor VIII products.

It was agreed that the phase I study could be performed in Dundee on condition that haemophilia nurses and doctors would be in attendance.

Dr Stewart agreed to discuss time-scales etc with DDS and to check the position with regard to indemnity for any reactions which may occur while at Dundee. Dr Stewart also agreed to produce a protocol for the Phase I study which would be submitted to each local Ethics Committee, and the Ethics Committee of Tayside Health Board.

Dr Ludlam was very keen that Phase II studies should be conducted with indemnity as set out in the ABPI guidelines. It was agreed that the Phase II study should be performed with the first infusion occurring in a bleeding or non-bleeding patient. Subsequent follow up would consist of monthly clinical examination, monthly LFT's, recording of any adverse events and patient diary records. Out-of-pocket expenses would be supplied for patient travel etc for attendance at haemophilia centres which is outwith their normal care.

Dr Lowe pointed out, that while we all want purer factor VIII products, it is essential that yield is maintained as we all want to maintain self sufficiency in addition.

Dr Ludlam then asked Dr Perry how much plasma PFC could currently process. Dr Perry replied that due to current problems increased intake of plamsa in PFC could not be justified. However the problems are finally being recognised and it is anticipated that corrective action will be taken within the near future.

Theoretically, PFC can handle 90 tonnes of plasma per year, but this is dependant on particular investment, including increased warehousing, freeze drying etc. Current operating capacity is 50 tonnes per year. Dr Ludlam enquired whether there would be sufficient plasma available if the capacity of PFC were increased. Dr Perry pointed out that it was planned to introduce the use of optimal additive solution in RTCs and it was predicted that this could yield some 20 tonnes extra of plasma per year.

Dr Ludlam pointed out that there had been a shift in international opinion towards high purity factor VIII in the last six months and the Haemophilia Society were continually monitoring trends with a consequence that Scotland was being compared with England. Dr Perry stated that increasing the purity of the factor VIII product is a central portion of the PFC development programme but in his opinion some of the attitude prevelant at the moment are not scientific.

Dr Ludlam commented that variable vial unitage, which can be between 160-300 international units per vial, is a real problem and no other pharamceutical is so variable. He also stated that in his opinion increased usage may be partially due to increased unitage per vial, as the tendency was to prescribe a number of bottles per patient. Dr Perry agreed that this was a problem but that it was very difficult to correct until the new product was in place as much of the variability was due to variation in activity loss during the heat treatment.

Dr Ludlam enquired what the fallback position would be if 2 cases of Non-A, Non-B hepatitis occur with the PFC product heated at 80°C for 72 hours (according to current ICTH guidelines, such an event should lead to discontinuation of a clinical trial). Dr Foster pointed out that with the new product there is more scope for the introduction of other virucidal processes as the higher purity will make the product more amenable to such treatments. Dr Perry reiterated that in a purer product, heat treatment is likely to be more effective. Dr Ludlam returned to his previous point and asked, if it would be possible to continue to use the PFC factor VIII for 9 months after it had been implicated in hepatitis transmission, while we await the development of a new purer factor VIII or should the Haemophilia Directors at that point, switch to a commercial product which had not been implicated in hepatitis transmission. It was agreed that in such an event, the decision rests with the Haemophilia Directors.

Dr Foster pointed out that higher temperature or a different formulation could be used to effect higher virus kill. If considered necessary solvent-detergent treatment could be introduced in addition to heat treatment. Dr Ludlam asked Dr Perry about the national stock, Dr Perry commented that this was about 1 million international units and consists of material at three stages - factor VIII is available for issue at PFC - material which will be available for issue in the near future and an estimate of what is currently held at the RTCs. He also pointed out that it was an objective to have 2 million international units stock available by 31 March 1989.

6. DISTRIBUTION OF MINUTES

It was agreed that minutes of the meeting should in future be distributed to members of the working party and to Dr Hepleston, Ninewells Hospital, Drs Dawson and Bennet, Aberdeen Royal Infirmary Dr Taylor in Raigmore Hospital, each Regional Transfusion Director, and Dr MacIntyre at the Scottish Home and Health Department.

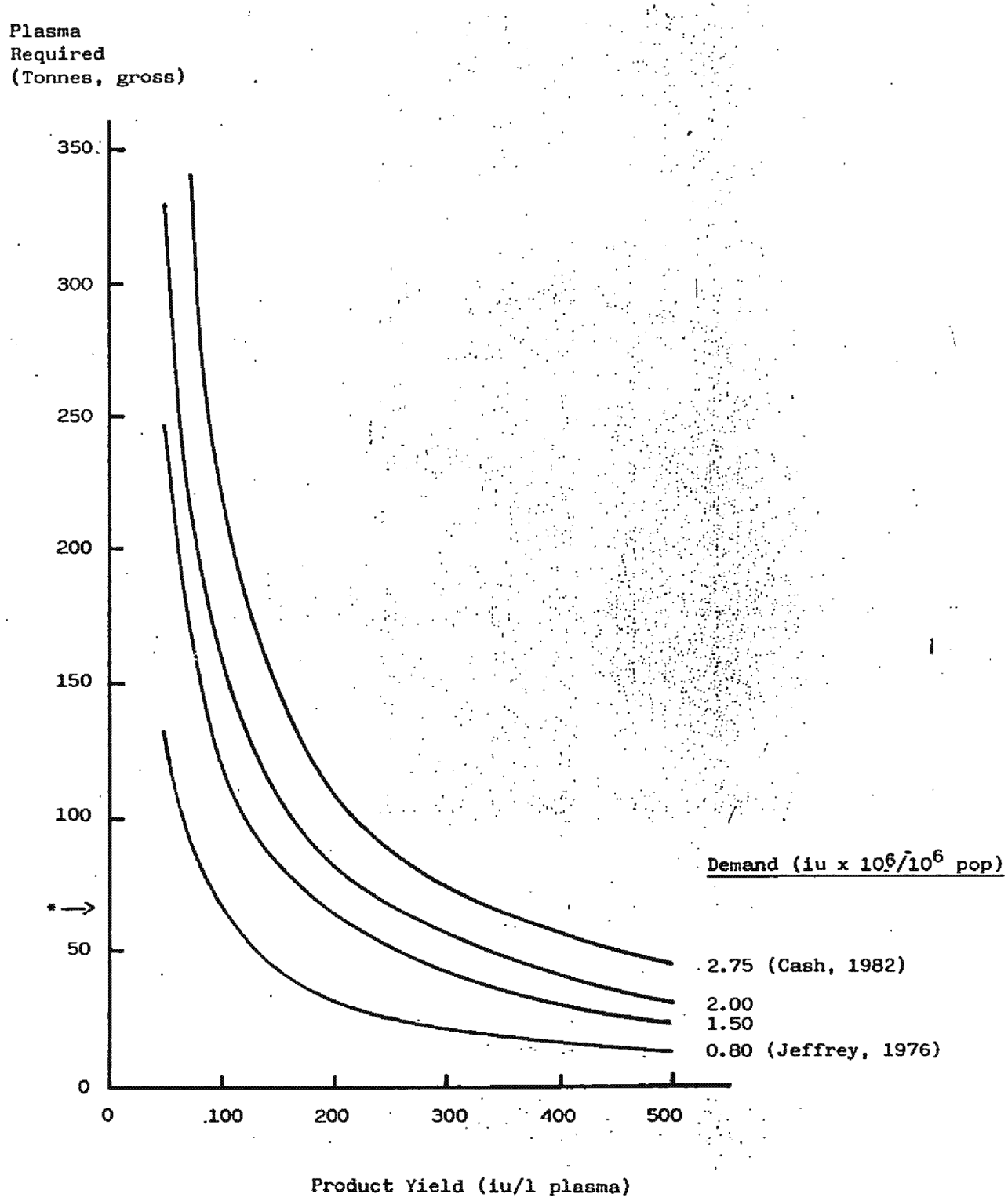
7. CONCLUSION

Dr Lulam thanked the members for their contribution and the meeting was closed.

APPENDIX I

FIG 2

QUANTITY OF FFP REQUIRED TO MEET THE DEMAND FOR FVIII IN SCOTLAND AND NORTHERN IRELAND



* INPUT OF FFP (78% 8hr and 22% 18hr) TO PFC IN 1986-87

APPENDIX II

DEVELOPMENT SCHEDULES FOR NEW SNBTS FACTOR VIII

Jan 89	*Phase 1	- Recovery/half Life/ pharmacokinetic study	8 Patients
Feb 89	*Phase II	- Clinical experience efficacy study (1st infusion under hospital care)	10 Patients
June 89		Commence routine manufacture Submit for PV variation	
Sept 89		Product Licence/routine use commence PUP study	

* Phase I and II studies will be performed with a pilot batch.

All patients who are enrolled in either study will remain in a long term follow-up study which will continue until the product is licensed.

APPENDIX III

IDEAL REQUIREMENTS FOR PHASE I STUDY
January 1989

Objective:	To compare the recovery and pharmacokinetic parameters of the new FVIII product with those of Z8.
Patients:	Eight non-bleeding, (preferably anti-HIV negative) severe haemophiliacs, who have not received Factor VIII, cryoprecipitate or FFP for at least 5 days.
Batches:	A single batch of SNBTS new FVIII compared with a batch of Z8.
Dose:	25 u/kg with the aim of achieving a post-infusion plasma concentration of approximately 0.5IU/ml.
Sampling Schedule:	Samples taken at: 0h,15 mins, 30 mins 1h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 20h, 24h. Samples to be immediately frozen.
Laboratory analysis:	All samples to be analysed at two laboratories for factor VIII c, factor VIII cAG and vWF:Ag. Factor VIII c to be determined by both one and two stage assays.
Assessments:	Inter individual differences in (i) half life, (ii) area under the elimination curve, will be compared.
Renumeration:	As the individuals' will be volunteers, consideration should be given to paying them for inconvenience/discomfort at the rate normally paid to volunteers.
Publication:	The results will be submitted for publication.
Indemnity:	Volunteers will be indemnified against injury by the SHHD as agreed previously, under the terms of the ABPI guidelines.
Location:	Due to the demands placed on the volunteers and medical staff involved in sample collection, it is not considered appropriate to perform the study in Haemophilia Centres. It therefore is proposed subject to suitable funding, to have the study performed at a professional clinical pharmacology unit eg Drug Development (Scotland) Ltd.