CAL12(140211)

Draft Witness Statement AIDS/HIV and Self Sufficiency in response to request of

23rd September 2010.

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(submitted to CLO 14th Feb 2011)

This witness statement attempts to provide a chronology in relation to the development of my knowledge about HIV/AIDS and the treatment of individuals with haemophilia with clotting factor concentrates. I have cross referenced my text to the Schedule (Schedule230910) which accompanied the requesting letter of 23rd September 2010.

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Background

A summary of 'HIV Infection in Haemophilia' as a draft Expert Report was prepared by me for the impending litigation in England and Wales. It sets out my view of the history as it appeared to me in 1990 (Appendix 1).

1. Definition of AIDS

In the early 1980s AIDS was a disorder defined as a clinical condition associated with opportunistic infections (e.g. Pneumocystis carinii pneumonia) or Kaposi's sarcoma in individuals without known reason for immune suppression. There was no laboratory diagnostic test. The definition was set out in MMWR (1) and is quite restrictive. Also described are a number of less specific features of the condition which may be associated, e.g. lymphadenopathy and weight loss. These less specific features had potentially many causes and it was therefore uncertain whether they were part of 'AIDS' or not. This is important because some of the potential viral (non-HIV) and other potential causes of AIDS could cause some of these symptoms and clinical signs, e.g. there are many viruses, and other stimuli of the immune system which were considered as causes of AIDS, which result in lymphadenopathy or changes in the immune system. This is also important because it was very uncertain as to whether the very first cases of AIDS in haemophiliacs represented the 'tip of an iceberg' or not – e.g. the majority of patients had 'immune suppression' (cause unknown) and it was very uncertain what proportion would develop into clinical AIDS. This lack of ability to accurately define AIDS very much added to the uncertainties in 1982 – 1984.

2. Potential causes of AIDS

In the early 1980s there were many potential aetiological agents which were considered to be possible causes of AIDS. The aetiological agent would have to explain its occurrence in diverse groups of individuals; homosexual men, haemophiliacs, Haitians, central Africans (both men and women), intravenous drug abusers and a small number of individuals who did not belong to any of these diverse risk groups. Among the possible aetiological agents were

I. An AIDS-causing virus – but what was it and where had it come from? If so why had no haemophiliacs in Germany, where large amounts of US commercial concentrates were used, developed AIDS by 1983?
II. A previously known virus which had mutated to a virus which caused immune suppression, e.g. hepatitis B virus
III. A virus known to cause immune suppression, e.g. CMV or EBV, which may have become more 'virulent'

IV. 'Antigen overload', e.g. semen in the rectum of homosexual men and non-factor VIII/IX proteins in clotting factor concentrates used to treat haemophilia.
V. 'Recreational drugs', e.g. amyl nitrate and isobutyl nitrate

Even after there was general agreement (in the second half of 1984) that HTLVIII was the probable cause of AIDS, there was very considerable uncertainty as to how to interpret an anti-HTLVIII positive (and negative) result in an individual person. Furthermore initially there was much uncertainty as to whether HTLVIII was the sole cause of AIDS or whether other co-factors were required. Even up to 1996, reputable scientific and medical journals were giving publication space to non-viral pathogeneses for AIDS (2).

3. Definition of Commercial blood products

A commercial blood product for this witness statement is considered to be one which is manufactured by a non-NHS facility. It should be noted that as well as human factor VIII and IX concentrates, other human clotting factor concentrates, e.g. Feiba, and non-human clotting factor concentrates, e.g. porcine factor VIII, are also commercial concentrates for which there was no NHS manufactured equivalent. Porcine VIII and Feiba were both licensed and used to treat haemophiliacs who had inhibitory antibodies to factor VIII.

4. Change of therapeutic policy

When a change in therapeutic policy, in relation to the appearance of AIDS in haemophilia, was being considered, it was necessary to consider the perceived risks of the existing treatment, versus the possible risks and acceptability of the proposed new therapeutic arrangements. During the second half of the 1970s until the mid-late 1980s, the commonest cause of death amongst UK haemophiliacs was bleeding, especially into the brain, and between 8 and 19 patients died annually in the UK from haemorrhage (3;4). This was despite the then existing consumption of clotting factor concentrate. Intracranial bleeding in 'untreated' severe haemophilia is often spontaneous and by the time the patient reaches hospital very severe brain damage has often occurred. Patients receiving concentrate therapy for their haemophilic joint bleeds will be protected from intracranial bleeds for a day or two after concentrate infusion. Thus individuals receiving 'on demand' (as opposed to full prophylactive) therapy will therefore be partially protected from these catastrophic bleeds.
If the amount of concentrate used had decreased, in response to the appearance of AIDS, it is likely that there would have been more deaths from bleeding. In addition there would have been very considerable morbidity if haemarrthroses went untreated. A typical bleed into a knee joint in someone with severe haemophilia will result in excruciating and protracted pain, usually requiring opiate analgesia, and bed rest for about 10 days. As a consequence of the disuse of the joint and bed rest there would be

atrophy of muscles around the knee and the weakened muscles would predispose to further haemorrhage.
The suggestion that patients should be switched from concentrate to cryoprecipitate would have resulted in their attendance at hospital for all treatment (i.e. abandoning home therapy). Where this was recommended in Cleveland, USA, it was not accepted by the patients (despite the apparently much higher risk in the USA of haemophiliacs developing AIDS in the early-mid 1980s). The proposed increase in use of cryoprecipitate, instead of concentrate, in the USA did not find favour amongst patients, and it was also associated with very significant HIV infection (5;6).

(Schedule230910/para1i) I was aware in 1982 of the first MMWR report of Pneumocyctis pneumonia in 3 haemophiliacs. The report states that 'the occurrence (of Pneumocystis carinii pneumonia) among the three haemophiliac cases suggests the possible transmission of an agent through blood products' which causes immune suppression.

5. In 1982/83 in the absence of any patient with an AIDS defining illness (see above), the only way to potentially investigate individuals to assess their possible susceptibility to developing AIDS was to assess their immune function by laboratory testing. By 1983 it therefore seemed important, as it did to many other haemophilia physicians, to investigate the immune status of patients under my care. The historical background to the assessment of immune dysfunction in haemophilia is set out in Appendix 2. This describes chronologically studies of immune function in non-haemophiliacs and haemophiliacs and some of the interpretations of the resultant data.

6. My studies of immune function were initiated in 1983. I was surprised to observe that many patients had immune abnormalities very similar to those reported from homosexual men and haemophiliacs residing in North America. The preliminary results were published in the Lancet (7) in response to a letter a month earlier which inquired if any studies had been undertaken in a non-AIDS endemic area of the world (8). Scotland was one such area in 1982 and 1983 as the vast majority of my patients had only been exposed to NHS concentrates and cryoprecipitate because of my policy of trying to avoid the use of commercial factor VIII and IX concentrates, which it was hypothesised could possibly be contaminated by a virus or other agent which gave rise to AIDS (see Appendix 3, Edinburgh Haemophilia Treatment Policy). At this time I enquired extensively throughout Scotland, of those who might see individuals with AIDS, e.g. GUM physicians, as to whether any such people had been encountered and I did not receive any positive reports. I therefore concluded that, at least in Edinburgh patients, the immune disturbances were due to a non-AIDS causing agent (and subsequently this was confirmed when anti-HTLVIII testing became available in late 1984 and virtually all of the patients were found to be negative in 1982 and 1983).

7. During 1982-1984 there was much debate about the cause of the immune abnormalities observed in haemophiliacs and amongst the possible causes were the following

    I. a previously un-described feature of haemophilia. The immune abnormalities were less pronounced in haemophilia B than haemophilia A.

II. an AIDS-causing virus which had ubiquitously infected many populations, including haemophiliacs in Scotland, resulting in immune disturbance, but which required a 'second event' to give rise to the clinical condition of AIDS.

III. 'antigenic overload' from the large amounts of non-factor VIII and IX proteins in the concentrates. This was particularly the case with the use of SNBTS concentrates (and cryoprecipitate) which were of low purity and contained large amounts of non-factor VIII proteins, including immunoglobulins. In the late 1970s and early 1980s the amount of concentrate used by patients throughout much of the Western world had increased dramatically and it was possible that this could have 'overloaded' the immune system of recipients. This was potentially an attractive hypothesis because it would explain why the immune abnormalities were less profound in haemophilia B as factor IX concentrates were purer than those containing factor VIII.

IV. Mutant hepatitis B virus

V. A non-B hepatitis virus

VI. CMV, herpes simplex virus or other virus

8. **(Schedule230910/para1ii)** Budapest meeting in August 1982.
I did not attend this meeting and did not receive a copy of Dr Foster's report.

11. **(Schedule230910/para1iii)** UKHCDO AGM 13th September 1982
I attended the meeting and the Minutes probably reflect the discussion, i.e. that there had been a July MMWR report of 3 haemophiliacs with AIDS in the US and that Dr Craske was invited to look further into the situation.

1983

12. By the beginning of 1983 the cause(s) of AIDS was far from clear although the evidence for blood transmission was increasing with 10 cases in haemophiliacs in the US, and a child developing an 'AIDS-like syndrome' after a platelet transfusion from a donor who subsequently went on to develop AIDS. In January the National Haemophilia foundation in the US made recommendations and in March 1983 CDC also offered guidance to prevent transmission.

The situation, however, was not straight forward:

a. The AIDS in haemophiliacs appeared to be different from that which was sexually transmitted, e.g. Kaposi's sarcoma was a hallmark of AIDS in homosexual men and individuals in Africa, was not reported in haemophiliacs. It was therefore possible that the condition in these two groups had different aetiologies.
b. At this time there were no cases of AIDS reported in haemophiliacs in the UK and only a handful in mainland Europe. The finding of widespread immune disturbance in apparently well haemophiliacs in the US, England and Scotland questioned the relevance of these tests as surrogate markers of a viral aetiology of AIDS.

c. Why was AIDS appearing in Haitians – what was its aetiology?

d. Up to 5% cases did not apparently fit into known risk groups – what was their mode of acquisition of AIDS?

13. With this perspective it was argued that it would have been inappropriate to have 'banned' import of clotting factor concentrates from the US because of the harm that would have been experienced by patients because there was insufficient NHS concentrate or cryoprecipitate in the UK to treat patients to the level that they expected.

14. **(Schedule230910/para1iii)** Meeting St Andrew's House of SNBTS & Haemophilia Directors January 1983. The Minutes report discussion of AIDS. The letter and questionnaire I referred to I think was one sent out by Professor Bloom, Chairman UKHCDO, enquiring about whether we had any evidence of AIDS in our patients. It was sent to many haemophilia centres in the UK and mainland Europe. The result of the survey was published in the Lancet in June 1984 and at that time Professor Bloom concluded that 'the role of American concentrates in the causation of AIDS in European haemophiliacs must be regarded as unproven' because only 8 cases of AIDS were identified in Europe and many parts of the continent were using large amounts of American concentrates and were not identifying any cases of AIDS, e.g. Germany (9).

15. Articles in the New England Journal of Medicine of 13th January 1983 . In this issue of the Journal are two articles reporting immune abnormalities in US haemophiliacs (10;11). In the paper by Menitove et al it is reported that those in receipt of cryoprecipitate the T4/T8 ratio was normal compared to those who received concentrate in which 43% were abnormal. In the accompanying editorial Dr Desforges writes that 'it is time to consider (changing from concentrate to cryoprecceiptate) even though we may not have enough evidence to demand such a radical change' (12). She has partly based this proposal on the fact that the immune system of recipients of cryo appeared to be normal (compared to concentrate users) but we now know that the immune changes are not a good reflection of the presence of infection by HIV. She goes on to state that 'the numbers are too small for definitive comparison of the risks of different modes of treatment' to be

made. I am not aware, however, that she acted on her 'recommendation' and changed patients under her care from concentrate to cryoprecipitate.

16. **(Schedule230910/para2i)** Meeting 24th January at Heathrow was an opportunity for UK haemophilia physicians to receive further information about AIDS and what one company (Immuno) was doing to try and reduce hepatitis transmission by concentrates. According to the minutes I attended the meeting but I do not recall the presentations or discussion.

17. **(Schedule230910/para2ii)** New Scientist - small article linking AIDS to blood products was not read by me. It does not contain any information not available elsewhere.

18. The article by Ragni et al (13) describes two haemophiliacs who were feeling well but both had developed lymphadenopathy and had a range of immune abnormalities which were very similar to those found in haemophiliacs in non-AIDS areas, e.g. Scotland – these haemophiliacs had both evidence of T cell depression and lymph node and B cell activation (as evidenced by histology of the lymph node and raised immunoglobulin levels) but did not have AIDS. At that time they only had features of 'AIDS –related complex' or what the authors described as a 'form fruste' , i.e. lymphadenopathy and weight loss. In retrospect these two patients were almost certainly infected by HIV. The authors don't make any recommendations about changing treatment for patients.

19. MMWR on 4th March 1983 made recommendations for limiting the spread of AIDS in the US based on the assumption that is was caused by a blood and sexually transmitted virus (14). Endorsed guidance offered by NHF in January 1983 .

20. Lancet Editorial 2nd April 1983 sets on the then current understanding about AIDS and haemophilia (15). It refers to articles in Annals of Internal Medicine, one suggesting that 'the T-cell population abnormalities commonly seen in haemophiliacs may be the submerged part of an iceberg of which AIDS is the clinically obvious tip' (16). We now know that this is an oversimplification of the situation, some of the T-cell changes may have been due to an AIDS virus but we know, again from Edinburgh studies, that not all immune changes were due to a putative AIDS virus and that estimation of immune function could not be used as a surrogate marker for asymptomatic infection by an AIDS causing virus. The Editorial cites White and Lesesne's attempts to reduce concentrate use although they do not indicate whether this was achieved (17). The Editorial concludes that 'the reported cases do not constitute a strong argument for a change in treatment policy'

21. **(Schedule230910/para2vi)** Dr Galbraith's letter of May 1983 from the PHLS to DHSS recommending the withdrawal of concentrates manufactured from US collected plasma was never, so far as I recall, brought to the attention of UKHCDO. I think Dr Galbraith was incorrect in stating that the haemophiliac who had just been diagnosed with AIDS came from Cardiff, as the case when more fully reported was likely to have been from the Bristol area (18) The letter was passed to the Committee on the Safety of Medicines for the meeting on 13th July of the Biologicals Subcommittee. The CSM was the body

responsible for licensing medicines in the UK and ensuring that their continued use was reasonable. I do not recall the CSM making public recommendations about restricting use of concentrates.

22. **(Schedule230910/para2iv)** The UKHCDO meeting on 13th May 1983 was of Reference Centre Directors, of which I was one, and therefore I attended the meeting. The AIDS situation was discussed and resultant guidance on therapy was issued by Professor Bloom and Dr Rizza to all haemophilia centre directors on 24th June. Dr Galbraith's letter was not, so far as I recall, and the minutes do not record, discussed or brought to the attention of the meeting. It was probably typed on the possible 9th May and it is unlikely to have arrived and been read at the DHSS by three days later, let alone passed to Professor Bloom as Chairman, UKHCDO. I note in the letter that Dr Galbraith suggested a decision should be reached after a discussion with haematologists and virologists - I certainly was not involved in any such forum with his letter. Presumably the DHSS considered the CSM an appropriate forum. The letter was not brought to my attention by SNBTS colleagues.

    As a result of the discussion and recommendations at the Reference Centre Directors meeting I discontinued the small use of commercial human factor VIII concentrate for non-inhibitor patients in Edinburgh (see synopsis of patients treated with commercial concentrates, para 61).

23. **(Schedule230910/para2vii)** The letter of 24th June from Professor Bloom and Dr Rizza to me was in fact sent to all haemophilia directors in the UK and set out the recommendations to reduce the potential risk of AIDS transmission. It was therefore sent to all haemophilia directors in Scotland. Children in Edinburgh were already being treated with SNBTS concentrate as recommended in the guidance and commercial human factor VIII for treating non-inhibitor patients was discontinued. My recollection is that the perceived risk of AIDS being transmitted by plasma collected in Scotland where, at this time, there were no cases of AIDS within the population was small. I think there may have been some consideration to reverting to cryoprecipitate but this was not pursued because of the perceived low risk of AIDS transmission and that the resultant therapeutic difficulties which would have followed (see para 33)

24. **(Schedule230910/para2v)** I did not attend the SNBTS coordinating group on 24th May as I was not a member.

25. **(Schedule230910/para2vi – para4)** This paragraph presumably refers to the SNBTS Directors and factor VIII subcommittee meeting on 14th June. I did not attend as I was not a member.

26. In the early 1970s, I was aware of Professor Cash's work on vasopressin analogues (as he was one of the supervisors of my PhD research). As part of my platelet research, I undertook studies on vasopressin analogues' ability to cause platelet aggregation. I was therefore very interested when Professor Mannucci reported that one vasopressin analogue, Desamino – 8- D argenine vasopressin (desmopressin, DDAVP), could raise factor VIII levels in mild haemophilia and von Willebrand disease to levels sufficient to

allow surgery to be carried out safely (19) . At this time I was working in Cardiff with Professor Bloom and I continued studies on the use of desmopressin in haemophilia and vWD which were published (20) .

27. As a result of my interest and research in desmopressin I was invited give a talk on its use in haemophilia at the UKHCDO Scientific Meeting in Glasgow in September 1980. I was therefore very keen to, and did, promote its use, but also very conscious of its potential side effects especially of water retention and toxicity (resulting in convulsions in children and fluid overload in adults).

28. **(Schedule230910/para2viii)** I did not attend the WFH and WHO meeting at the Karlinska in June 1983 nor did I see Dr Foster's report.

29. **(Schedule230910/para2ix)** I did not see any communication from the Biological subcommittee of the CSM after its meeting in July. I am not aware of the constitution of the committee or who attended the meeting.

30. **(Schedule230910/para3)** UKHCDO meeting in Manchester 17th October 1983. I attended the meeting. I have reviewed paragraphs 9 and 10 in the minutes which are accurately summarised in the Preliminary Report (8.61 and 8.62).

31. **(Schedule230910/para3)** I was not aware of the WHO or Aarhus AIDS conferences in October and November 1983 and do no not remember receiving any synopsis or recommendations from either of these meetings.

32. **(Schedule230910/para3iii)** Haemophilia Society view about use of commercial factor VIII concentrates.

People with haemophilia had campaigned vigorously for access to concentrate so that they could have treatment at home. The substantial benefits of this have been summarised in my paper on Edinburgh Treatment Policy (3) and I had worked with SNBTS colleagues to acquire as much SNBTS product as possible for this. Because of the limited availability of SNBTS concentrate I had preferred to delay home treatment rather than give commercial VIII concentrate especially to young individuals.

The Haemophilia Society was clear in its view that patients should continue to use commercial VIII concentrate at least until the Summer of 1983 (see Haemophilia Society Annual Report). The Society met with Lord Glenarthur, Minister of Health at the DHSS, as it was keen to ensure a continued supply of concentrate even if it had to be imported from the US.

33. In Scotland my recollection is of a brief consideration of the possibility of reverting to cryoprecipitate but to do so would reverse the process of collecting as much plasma as possible for fractionation into factor VIII concentrate for which Scotland had

worked so hard to enable it to become self sufficient in factor VIII in 1983. Furthermore cryoprecipitate preparation requires considerable investment in equipment including centrifuges and fridges. At a time when there were no AIDS cases reported in the Scottish population (which was more static that in England and therefore at probable lower risk) it seemed reasonable to continue with the priority of manufacturing concentrate from Scottish donors. Even if Scotland had reverted to cryoprecipitate for the treatment of haemophilia patients would still have become infected with HIV.

34. **(Schedule230910/para3iv)** I do not recall receiving any advice from the Geneva conference.

35. **Awareness of the evolution of AIDS in the Scottish population**.

Because of my interest in the cause of immune dysfunction in people with haemophilia in 1983, I made strenuous efforts to find out about whether any patients with AIDS had been diagnosed in Scotland and if so might any have been blood donors. I became aware of a sailor, who might have had AIDS and who had been transiently in one of the Scottish ports, but I was assured that he had never been a blood donor. The man who returned from living in Africa and who was reported to have died of AIDS in 1982 would never have been well enough to be a blood donor (as he returned symptomatic from Africa).

I note that the SCIEH report (Appendix 4 of the Penrose Preliminary Report) records that (apart from the above AIDS case of African association) the first 3 cases of AIDS in Scotland were diagnosed in 1984. It is not clear when these were reported to SCIEH as the table appears to contain data related to 'year of diagnosis' rather than 'year of reporting' – this appears to be the case because of the 'HIV-infected person data' which starts in 1981 could not have been included until the autumn of 1984 at the very earliest (and likely much later).

I note the 'unnamed GU specialist' quoted in the Bennet/Pettigrew thesis indicated the presence of AIDS in GUM clinics in 1983. It would be useful to have evidence for this (if so why were they not reported to SCIEH) because my enquiries did not reveal any evidence of 'AIDS' at this time.

36. **(Schedule230910/para4) Use of commercial concentrate in early 1984**

In Edinburgh commercial factor VIII concentrate use was discontinued in May 1983 (except for treatment of non-inhibitor patients). In April 1984 30,000 units were used to treat a patient who developed, at that time, unique clinical difficulties following surgery. His surgery and immediate post-operative period was covered with SNBTS factor VIII concentrate but in the latter part of his post-operative period he became unwell and because of his clinical difficulties he was changed to commercial factor VIII concentrate.

Two further patients received commercial human factor VIII concentrate in 1983 for treatment of acute bleeds. Both these individuals had anti-factor VIII inhibitors, required large doses of concentrate, and therefore required a higher purity which was possible only with a commercial concentrate.

37. **Heat treated clotting factor concentrates in Scotland in 1984**

On 10th December 1984 UKHCDO Reference Centre Directors and senior NBTS and SNBTS staff met at Elstree to consider, amongst other, my evidence (from the 'implicated' batch) that HIV infection had been found in the UK blood supply. There was protracted discussion about whether or not to recommend the use of heat treated concentrates. Although some heated concentrate was said to have been used in the US, there was very little knowledge, or experience, of using such concentrates in the UK. Because it was generally known that I wished to avoid using commercial concentrates, in general, I had not been approached by commercial producers to trial heated concentrates. The commercial manufactures were not generally forthcoming about their heat-treated products (for reasons of commercial confidentiality). The concern about moving to heated products was two-fold. Firstly there was very little evidence for the efficacy of heat treatment in rendering HTLVIII non-infectious and there was evidence that it did not inactivate hepatitis viruses. Secondly there was concern that the antigenicity of the factor VIII protein might be altered leading to the development of anti-factor VIII antibodies in the recipients which might neutralise the transfused factor VIII resulting in it being impossible to arrest haemorrhage. Evidence for these concerns was raised by eminent immunologists in a letter to the Lancet in January 1985 (21) . Concern about the latter was vindicated subsequently in 1991 when there were two major tragedies when minor alterations in the manufacture of concentrate led to the development of anti-factor VIII antibodies in the recipients (22;23) .

The decision to recommend the use of heat-treated concentrates was made and the advice disseminated by way of a circular, dated 14th December 1984, to all haemophilia centre directors.

As a result of the decision to heat-treat concentrates SNBTS issued immediately concentrate dry heated at 68 degrees for 2 hours. All patients in Scotland were asked to return their stocks of home treatment and they were issued with heated product. Thus by the end of December 1984 all patients in Scotland were treated with heated product. As our subsequent monitoring studies demonstrated, there were no further transmissions of HIV, despite the retrospective discovery that some batches of SNBTS plasma had been contaminated with HIV (24) . This was a major success for patients in Scotland and the arrangements were ahead of those elsewhere in the UK and the majority of countries in the world.

38. **Towards self-sufficiency in Scotland in factor VIII concentrate**

Data collection on use of clotting factors use in Scotland.

Haemophilia Centres within Scotland report to UKHCDO each year their clotting factor use by product along with the number of patients treated. This system had been in existence since 1968 and provided insight into how much factor VIII was being used in the UK. The National Haemophilia Database was started in 1950, is now computerised, and holds a list of virtually all patients with haemophilia (with their severity and other data) in the UK. The information in this database has been invaluable for many purposes including the planning of factor VIII provision.

39. In Edinburgh in the 1970s and early 1980s information on each and every infusion of concentrate given at the Haemophilia Centre was recorded manually in a log book (with both a daily log of issues and also a page for each patient). The date, product, batch number, dose and reason for infusion were recorded. Issues of concentrate for home treatment were also recorded. Patients were supplied with forms to record their home use of concentrate which they were asked to return to the centre when they received their next batch of home treatment. This manual system worked well and required about 2 hours work per day for a clerical officer to maintain (this was the sole clerical assistance for data collection in the early 1980s).

40. Now in 2010 we have two fulltime staff to keep records of clotting factor use and the system has been computerised from about the mid 1980s. Currently we use the UKHCDO HCIS (Haemophilia Clinical Information System) database which is networked between the East of Scotland Haemophilia Centres. The information about use of clotting factor use (commercial and NHS) was made available to SNBTS annually.

41. One of the limitations of the UKHCDO system is that it only records concentrate used in, or under the auspices of, a Haemophilia Centre. It was only in the early 1980s in Edinburgh that there was a general acceptance that all patients with haemophilia should be registered and treated in the haemophilia centre. Prior to this some patients were treated in other hospitals not necessarily by a haematologist and their clotting factor use would therefore not be recorded by the haemophilia centre and hence UKHCDO database.

42. The other source of information on clotting factor use was that derived from SNBTS.
    Commercial concentrates for use in Edinburgh were purchased through, and stored in, the SNBTS blood bank at the Royal Infirmary and data on use would therefore have been readily available to SNBTS.
    For PFC manufactured products there were a number of different ways in which concentrate 'use' could be recorded. One measure is units of factor VIII manufactured. However, following manufacture each batch is 'held' while quality control and assay checks are made before it is available for use in patients. Upon 'release' it was sent to SNBTS regional centres where it was either stored and issued direct to patients (as in Edinburgh, Dundee, Aberdeen and Inverness) or sent to hospital blood banks (as in the West of Scotland) for issue to patients. In the East of Scotland, therefore, SNBTS had direct access to patient use data.

43. As a prescriber of products the important factor VIII statistic was the amount of concentrate available in the SNBTS blood bank in the Royal Infirmary in Edinburgh, the 'monthly' deliveries from PFC and the certainty that there would be the anticipated delivery. At times, as is clear from the Preliminary Report, it was very much a 'hand to mouth' existence especially when there were production difficulties, or an unexpected surge in demand from patients bleeding, which was almost always unpredictable.

44. One issue which is important to note is that cryoprecipitate is used to treat many patients other than haemophiliacs. Unless it is clearly specified in SNBTS statistics that the cryoprecipitate use was for haemophiliacs only, it was probably being used in a range of other hospital patients with acquired bleeding conditions. A more accurate measure of cryopreceiptate use for haemophilia is that recorded for UKHCDO.

45. A further potential source of confusion is that UKHCDO statistics, until recently, were collected per calendar year whereas, I believe, SNBTS were recorded per financial year.

46. In Edinburgh it was agreed that commercial factor VIII concentrate would be bought on behalf of Lothian Health Board and stored in the SNBTS blood bank in the Royal Infirmary. SNBTS therefore had accurate information about purchases, stock and use. This arrangement was agreed with Lothian Health Board at a meeting in 1981. Subsequently in 1983 it was agreed to change the arrangements and for commercial concentrates to be stored in, and issued from, the Royal Infirmary Pharmacy (Appendix 4)

47. The difficulties experienced in assembling reliable factor VIII issue and use data was one of the important reasons for the establishment of the Factor VIII Working Party for Scotland and Northern Ireland, under my chairmanship, in 1987 and the subsequent employment of Dr R Stewart to assist the work of the committee.

48. I have always been a strong supporter of self-sufficiency as evidenced by my insistence, so far as possible, on avoidance of commercial factor VIII concentrates, and reluctance to allow patients under my care to take part in the early trials of heat treated commercial concentrates (Referenced in Penrose Preliminary Report). The Edinburgh Haemophilia Treatment Policy is set out in Appendix 3.

49. **Home therapy for haemophilia**

When I became responsible for the haemophilia service at the beginning of 1980 the majority of treatment at the Edinburgh haemophilia centre was with cryoprecipitate. This was in marked distinction to the rest of the UK where only about 15% of all factor VIII was given as cryoprecipitate. See below

		Cryo%	NHS conc%	Commercial%
UK	1980	15	25	60
Edinburgh	1979	65	35	0
Edinburgh	1980	40	55	5

This high use of cryoprecipitate was a direct result of the long term historical policy in Edinburgh not to use commercial factor VIII concentrates and SNBTS's inability to manufacture an adequate amount of concentrate for the perceived need. The direct result of this was that at the beginning of 1980 there were only 6 patients on home treatment out of a population of 187 patients registered with haemophilia A. Thus only 4% of Edinburgh patients had the benefit of home treatment . There was, therefore, very considerable pressure, from patients, when I took up my appointment at the beginning of 1980, for an increase in the home treatment programme. As a result of an increased availability of SNBTS factor VIII concentrate and the use of a small amount of commercial, it was possible to increase substantially the numbers of patients on home treatment over the succeeding few years as set out below.

Number of Edinburgh patients with haemophilia on home treatment

	No. on home treatment
• 1976	4
• 1977	7
• 1978	6
• 1979	6
• 1980	18
• 1981	20
• 1982	26
• 1983	37
• 1984	33
• 1985	39
• 1986	36
• 1987	40
• 1988	46
• 1989	47

50. **Clotting factor concentrate purity and potency**

In the Preliminary Report there is mention of concentrate purity and potency and I lay out below how, from my perspective, this was an important topic in the 1980s.

51. **Purity** is defined as unit clotting factor per milligram of total protein in the reconstituted vial, i.e., i.u./mg.

Potency is the concentration of clotting factor in the reconstituted vial, i.e., i.u./ml.

52. **Purity**

In the 1980s levels of purity could be defined as follows*

- Low <1 i.u./mg protein
- Intermediate 1-10 i.u./mg protein
- High >10 i.u./mg protein

*The definition of purity changed during the 1980s as products of increasing purity became available but for the purposes of this Statement the above categories are used.

Factor VIII is present in normal plasma in minute quantities (by weight) (approximately 100 picogram (ten thousandths of a gram) per ml plasma. In a clotting factor concentrate such as SNBTS NY there was about 0.3 units factor VIII per mg total protein, i.e. factor VIII protein represents about 1-2% of the protein in the concentrate the remainder being fibrinogen, fibronectin, immunoglobulin and other plasma proteins. These plasma proteins, some of which are present in large quantities in the starting plasma, can be viewed as unnecessary and potentially harmful 'contaminants'. During the fractionation process a small proportion of these proteins co-purify with factor VIII and in an attempt to increase the purity by altering the manufacturing conditions there is usually some loss of factor VIII.

From a manufacturer's perspective a low purity product usually maximises the yield of VIII from the starting plasma and this is highly relevant when trying to reach self-sufficiency (see letter from Dr Foster to Dr McClelland 17th August 1982, Preliminary Report para 10.113).

53. Purity in important to a physician and patient for the following reasons

I. Lower purity products are usually slower to dissolve when water is added to the vial and there is a greater chance of aggregates remaining in the solution.

II. Lower purity products are more likely to result in 'allergic' reactions because there are more 'contaminant' proteins present to which the recipient might

react. The lowest purity product is cryoprecipitate and this results in the highest frequency of reactions.

III. Lower purity concentrates may contain anti-blood group A and B antibodies which can react with the recipient's red cells to cause a haemolytic anaemia.

IV. The contaminant proteins may accumulate in the recipient and predispose to a haemorrhagic state. For example fibrinogen has a half life in the plasma of about 5 days which is about 10 times that of 12 hours for factor VIII. If factor VIII concentrate is being given twice daily, for example in the post operative period, to maintain the factor VIII level at a haemostatic level, the fibrinogen accumulates. Furthermore following a physiological stress, e.g. surgery, the body responds by increasing the synthesis of fibrinogen which raises further its plasma concentration (acute phase reaction). Fibrinogen is one of the main contributors to the viscosity of the blood and hence if the fibrinogen rises the blood becomes more viscous and predisposes to an acquired bleeding state. Thus purity becomes an issue when VIII infusions are being given over a prolonged period, e.g. after major orthopaedic surgery.

54. Purity became a particular issue in the 1980s because

- It was considered possible that the contaminant proteins, especially the immunoglobulins, might be responsible for the immune modulation that I and others were observing in haemophiliacs who were probably not infected with an AIDS-promoting virus. In the early days of AIDS it was considered that large amount of these proteins might predispose to, or be the cause, of AIDS.

- There was, and very much still is, a possibility that these contaminant proteins might be beneficial by modulating the immune system and reducing the development of antibodies to the transfused factor VIII. Anti-factor VIII antibodies arise in about 25% of small children with severe haemophilia and are currently the most feared and severe complication of haemophilia. This is the subject of a current major European trail of factor VIII (Sippet.org).

- In the late 1980s there were suggestions that lower purity concentrates were associated with a more rapid progression to AIDS in those infected with HIV (di Biasi, 1991 – summarises previous presentations from 1989 onwards). One possible mechanism was that 'impurities' in the concentrates might stimulate immune cells harbouring the HIV virus resulting it more virus being released into the circulation. For this reason high purity products became recommended for infected patients although the evidence was not substantial and it seemed

prudent, if there was possible benefit, to give patients the possibility of a better HIV outcome. With colleagues, I took the opportunity to study this possibility by measuring the immune parameters in patients when Scotland switched from an intermediate purity concentrate to the high purity concentrate in the early 1990s. This study did not reveal any change in the immune tests after the switch of concentrate (25) .

- Low purity concentrates might be associated with the development of pulmonary hypertension (26).

55. **Potency**

Potency is important because it relates to the volume of concentrate which needs to be infused, i.e. higher potency concentrates require a lower infusion volume. This is particularly important when treating babies and small children, as giving intravenous injections is often a substantial technical challenge. The early factor VIII concentrates had a potency of about 5-10 units/ml, whereas currently available products have a potency of 100-500 units/ml.

To a large extent purity and potency are bound up together because lower purity concentrate requires a larger volume of diluent for reconstitution to solubilise the contaminant proteins (especially fibrinogen) and this results in a lower potency product.

56. The level of purity of the factor VIII concentrate available in the early 1980s in Scotland did result in difficulties in treating patients;

    a. In 1980 two patients who underwent hip replacements in Edinburgh both developed a secondary haemorrhagic state because of the high fibrinogen content of the concentrate. It was for this reason that commercial concentrate was used in these two patients.

b. Allergic reactions to low purity concentrates were a clinical problem in a small number of patients

c. During the 1980s, as different fractionation methods were used by SNBTS, solubility of the concentrates became a clinical issue from time to time as documented in the Preliminary Report.

d. In Scotland, with the development of the high purity, ion-exchange purified factor VIII concentrate, in conjunction with the fractionation plant in Lille, the purity and potency issues were addressed and these ceased to be clinical issues after the introduction of Liberate in the early 1990s

57. General arrangements for interactions between myself and SNBTS in the early 1980s.

When I took up my appointment as consultant haematologist and director of the Haemophilia Centre in 1980, it was my responsibility to provide for, and improve, the arrangements for the individuals with haemophilia and other heritable bleeding disorders. At that time I had many other responsibilities including treating patients with leukaemias, lymphomas and a broad range of other haematological disorders. I estimate that about a quarter of my time was devoted to providing the haemophilia service which was not only seeing patients but also involved overseeing the running of a coagulation laboratory for the hospital which provided a regional reference service. I was also responsible for ensuring that the links for patients to other services, e.g. orthopaedics and dentistry, worked promptly and smoothly. There were the administrative and managerial arrangements to attend to for ensuring an adequate supply of appropriate concentrates. The only clinical assistance I had was one haematology registrar (who had a broad range of other clinical and laboratory activities) and a clerical officer for about 2 hours a day to record manually clotting factor usage.

58. Cryoprecipitate and clotting factor concentrates, as most were manufactured by SNBTS, were initially stored at the hospital blood bank, which was also managed by SNBTS. They were issued to patients mostly in response to telephone requests from clinical staff.

59. On a day to day basis I interacted with Dr Frank Boulton, Consultant in Blood Transfusion and Dr Brian McClelland, director of South East Scotland Blood Transfusion Centre. They were responsible for maintenance of the SNBTS manufactured stocks of clotting factor concentrates. Commercial concentrates were ordered by SNBTS under an agreement with Lothian Health Board (Appendix 4) and also stored in the SNBTS-run hospital blood bank.

60. When I took up my appointment there was by a paucity of factor VIII concentrate compared to elsewhere in the UK (see para 49) and as is set out in the Preliminary Report I wished more concentrate, particularly to enable additional patients to have home treatment. This led to tensions between myself and colleagues in SNBTS because I could not always predict with accuracy what the demand would be for concentrate, as bleeds in patients occurred spontaneously, with resultant quiet and busy periods, and because the availability and delivery of concentrates from PFC was subject to a degree of unpredictability, for reasons set out in the Preliminary Report. It felt like a 'hand to mouth' existence with anxiety on both sides; viz that SNBTS might not be able to deliver what I anticipated and I might have an increased unpredicted need which might be difficulty to meet. On at least one occasion the stock of factor VIII was exhausted in the hospital blood bank and I was left having to telephone one evening the duty officer for PFC to get stock delivered urgently for a bleeding patient. The stress in the system was perhaps reflected by Dr Boulton preparing very formal minutes after two meetings at which the supply situation was discussed (para 10.112 minutes of meetings, ref 140 and 142). Furthermore it seems

that there were perhaps differences of opinion about the appropriateness of my expectations between Professor Cash as Medical Director, Dr Frank Boulton and Mr John Watt; the letter of 28th October 1982 (ref 138) indicates clearly that my expectations were reasonable especially given the pro-rata distribution of VIII concentrate depending upon FFP supply to PFC which had been agreed some time previously, and concern was expressed about the ability to supply because of possible industrial action at PFC.

Thirty years on it is difficult, with the information currently available, to reconstruct accurately and in detail the expectations, discussions and negotiations over the supply of clotting factor concentrate. It seems to me, however, that both producer and consumer were in dialogue and trying to manage difficult situations as best as the circumstances would allow. There will always be tension where demand outstrips supply.

Overall I concluded that my standing both within SNBTS must have been reasonable or I would not have been invited to be an Honorary Consultant to the organisation in 1987. Similarly, as I was invited by SHHD to convene and chair the factor VIII Working Party for Scotland and Northern Ireland, which was a tripartite committee of senior representatives of SHHD, SNBTS and haemophilia directors, I assumed that my opinions and actions were considered of value as was my leadership of haemophilia activities in Scotland.

61. **Commercial Factor VIII concentrate use by the Edinburgh Haemophilia Centre.**

Appendix 5 lists the patients (annonymised) who received commercial factor VIII concentrate, the patient's clinical situation and the concentrate received each year. The use is summarised below

1980 – 3 patients received commercial human factor VIII concentrate

Two patients (A & B) developed the hyperviscosity/hyperfibrinogenaemia syndrome (because of the low purity of the SNBTS concentrate) following hip replacements and therefore required commercial concentrate of higher purity. One of these patients went on to receive commercial concentrate (along with his brother) for home therapy because they were both very keen to have such an option as they lived an appreciable distance from Edinburgh and having severe haemophilia had frequent bleeds. Neither patient became infected with HIV from the commercial concentrate (but both became HIV positive from the SNBTS 'implicated batch' in 1984).

One patient (C) received commercial concentrate because of apparent non-therapeutic response to SNBTS factor VIII concentrate. He required protracted treatment for a severe haemarrthrosis. He responded therapeutically to the commercial concentrate. On retrospective testing in late 1984 he was found to have become infected with HIV as a result of the commercial concentrate.

1981 – 6 patients received commercial human factor VIII concentrate

One of the hip replacement patients (patient A above) continued on commercial VIII at the beginning of 1980. After he left hospital he continued on commercial concentrate for home treatment. Early in 1981, his brother (D), started on home therapy with commercial VIII because he lived a long way from the Royal Infirmary.

The non-responder (C) to SNBTS VIII continued on commercial VIII in 1981 to cover surgery on joint affected by the protracted and recurrent bleeding.

One patient (E), a visitor from abroad, received commercial VIII concentrate because he had been treated with this form of treatment lifelong.

One patient (F), who had frequent reactions to treatment, received a single injection of a purer commercial VIII concentrate. Unfortunately he reacted to it also. He remained HIV negative (but became infected from the 'implicated' SNBTS batch in 1984).

One patient (G) with an inhibitor to factor VIII was treated with large doses of VIII for a serious bleed. He remained HIV negative.

One patient (E), a resident from another European country, came to Edinburgh for review of his haemophilia. As he had been on commercial VIII previously this was continued whilst he was in Edinburgh. With retrospective testing he was found to be HIV positive in 1981 (i.e. prior to receiving treatment in Edinburgh).

1982 - 2 patients received commercial human factor VIII concentrate

The two brothers (A & D) referred to above continued on commercial VIII for home treatment.

1983 – 6 patients treated with commercial human factor VIII concentrate. No non-inhibitor patient was given commercial VIII concentrate after the end of May.

The two brothers (A & D) referred to above continued to receive commercial VIII.

One of the inhibitor patients (G) referred to above received further treatment for bleeding.

The patient (C) who received commercial VIII in 1980 for non-response to SNBTS VIII received further treatment.

A patient (I) from abroad had previously received commercial VIII. Retrospective testing revealed that he was HIV positive before his arrival in Edinburgh.

A patient (J) on SNBTS VIII was issued with commercial VIII to take away for home treatment. He remained HIV negative.

1984 – 1 patient received commercial human factor VIII concentrate

The patient (K) received commercial VIII because of a unique and complex clinical situation. He became infected with HIV by the SNBTS 'implicated' batch.

1985 – No patients were treated with commercial human factor VIII concentrate

1986 – No patients were treated with commercial human factor VIII concentrate

62. **Summary** –of commercial human factor VIII concentrate, numbers of patients and HIV outcome

Clinical situation	No.	HIV outcome
• Post-op hyperviscosity/hyperfibrinogenaemia	2	1 remained HIV neg 1 HIV infected by SNBTS implicated batch 1984
• 'Non-responder' to SNBTS VIII in 1981	1	HIV infected by VIII 1981
• Complex clinical state in 1984	1	HIV infected by SNBTS implicated batch 1984
• Allergic to treatment	1	HIV infected by SNBTS implicated batch 1984
• Inhibitor patients	1	Remained HIV neg
• Home treatment	2+1*	2 HIV infected by SNBTS implicated batch 1984
• Previous recipients of commercial VIII	2	Both HIV positive before arrival in Edinburgh

*This patient was one of the two patients who received commercial concentrate following surgery – listed above

Thus out of 9 patients susceptible HIV, one became infected probably by commercial human factor VIII concentrate in 1981 as a result of treatment in Edinburgh, and four patients seroconverted to the SNBTS 'implicated' batch in 1984.

Reference List

(1) Pneumocystis carinii pneumonia among persons with hemophilia A. MMWR Morb Mortal Wkly Rep 1982 Jul 16;31(27):365-7.
(2) Duesberg P. Commentary: non-HIV hypotheses must be studied more carefully. BMJ 1996 Jan 27;312(7025):210-1.
(3) Rizza CR, Spooner RJ. Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976-80: report on behalf of the directors of haemophilia centres in the United Kingdom. Br Med J (Clin Res Ed) 1983 Mar 19;286(6369):929-33.
(4) Rizza CR, Spooner RJ, Giangrande PL. Treatment of haemophilia in the United Kingdom 1981-1996. Haemophilia 2001 Jul;7(4):349-59.
(5) Ratnoff OD, Lederman MM, Krill C, Jr., Pass LM, Ross CE. Hemophilia and the acquired immunodeficiency syndrome. Ann Intern Med 1985 Mar;102(3):412.
(6) Ratnoff OD. Some complications of the therapy of classic hemophilia. J Lab Clin Med 1984 May;103(5):653-9.
(7) Ludlam CA, Carr R, Veitch SE, Steel CM. Disordered immune regulation in haemophiliacs not exposed to commercial factor VIII. Lancet 1983 May 28;1(8335):1226.
(8) Gordon RS, Jr. Factor VIII products and disordered immune regulation. Lancet 1983 Apr 30;1(8331):991.
(9) Bloom AL. Acquired immunodeficiency syndrome and other possible immunological disorders in European haemophiliacs. Lancet 1984 Jun 30;1(8392):1452-5.
(10) Lederman MM, Ratnoff OD, Scillian JJ, Jones PK, Schacter B. Impaired cell-mediated immunity in patients with classic hemophilia. N Engl J Med 1983 Jan 13;308(2):79-83.
(11) Menitove JE, Aster RH, Casper JT, Lauer SJ, Gottschall JL, Williams JE, et al. T-lymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. N Engl J Med 1983 Jan 13;308(2):83-6.
(12) Desforges JF. AIDS and preventive treatment in hemophilia. N Engl J Med 1983 Jan 13;308(2):94-5.
(13) Ragni MV, Lewis JH, Spero JA, Bontempo FA. Acquired-immunodeficiency-like syndrome in two haemophiliacs. Lancet 1983 Jan 29;1(8318):213-4.
(14) Prevention of acquired immune deficiency syndrome (AIDS): report of inter-agency recommendations. MMWR Morb Mortal Wkly Rep 1983 Mar 4;32(8):101-3.
(15) Acquired immunodeficiency in haemophilia. Lancet 1983 Apr 2;1(8327):745.
(16) Curran JW, Evatt BL, Lawrence DN. Acquired immune deficiency syndrome: the past as prologue. Ann Intern Med 1983 Mar;98(3):401-3.
(17) White GC, Lesesne HR. Hemophilia, hepatitis, and the acquired immunodeficiency syndrome. Ann Intern Med 1983 Mar;98(3):403-4.
(18) Daly HM, Scott GL. Fatal AIDS in a UK haemophiliac. Lancet 1984 Jan 7;1(8367):44.
(19) Mannucci PM, Ruggeri ZM, Pareti FI, Capitanio A. 1-Deamino-8-d-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrands' diseases. Lancet 1977 Apr 23;1(8017):869-72.
(20) Ludlam CA, Peake IR, Allen N, Davies BL, Furlong RA, Bloom AL. Factor VII and fibrinolytic response to deamino-8-D-argenine vasopressin in normal subjects and dissociate response in some patients with haemophilia and von Willebrand's disease. Br J Haematol 1980 Jul;45(3):499-511.
(21) Bird AG, Codd AA, Collins A. Haemophilia and AIDS. Lancet 1985 Jan 19;1(8421):162-3.
(22) Peerlinck K, Arnout J, Gilles JG, Saint-Remy JM, Vermylen J. A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate. Thromb Haemost 1993 Feb 1;69(2):115-8.

(23) Peerlinck K, Arnout J, Di GM, Gilles JG, Laub R, Jacquemin M, et al. Factor VIII inhibitors in previously treated haemophilia A patients with a double virus-inactivated plasma derived factor VIII concentrate. Thromb Haemost 1997 Jan;77(1):80-6.

(24) Cuthbert RJ, Ludlam CA, Brookes E, McClelland DB. Efficacy of heat treatment of factor VIII concentrate. Vox Sang 1988;54(4):199-200.

(25) Hay CR, Ludlam CA, Lowe GD, Mayne EE, Lee RJ, Prescott RJ, et al. The effect of monoclonal or ion-exchange purified factor VIII concentrate on HIV disease progression: a prospective cohort comparison. Br J Haematol 1998 Jun;101(4):632-7.

(26) Goldsmith GH, Jr., Baily RG, Brettler DB, Davidson WR, Jr., Ballard JO, Driscol TE, et al. Primary pulmonary hypertension in patients with classic hemophilia. Ann Intern Med 1988 Jun;108(6):797-9.