Methodology for collation of Scottish HCV & NANB data for PI

1. The starting data received from UKHCDO database included patient names and treatment details (within and outwith Scotland) for all patients registered or treated in Scotland prior to 1990, from approximately 1970. It has been assumed that coagulation factor treatment from 1990 onwards would not have caused HCV whilst coagulation factor treatment prior to 1988 was almost uniformly associated with HCV infection in patients receiving PFC manufactured factor VIII. In addition based on previous observations it was known that patients treated with cryoprecipitate also commonly became infected with HCV – for the purposes of this exercise patients who had received cryoprecipitate prior to 1990 were also assumed to have contracted HCV unless they had subsequently been tested and proven negative (see later). This list included approximately 715 patients. However it did not identify which patients were known to be HCV positive, as this information is not recorded on the UKHCDO database.

2. The aim was to identify all patients who have become, or have possibly become, infected with HCV due to coagulation component treatment administered by NHS Scotland.

3. For the purpose of this exercise we assumed that the earliest treatment with Factor concentrate or cryoprecipitate or plasma (FFP) could possibly have transmitted HCV.

4. The following patients and their treatment episodes were excluded from the list (by hiding relevant rows in the excel spread sheet):

    a. All patients on the list whose first treatment was outwith Scotland. Where the earliest year of treatment included treatments within and outwith Scotland these patients were retained on the list as it was not possible to determine the sequence of treatments during any one year. This left approximately 544 patients on the list whose first treatments were, or could have been, in Scotland during the HCV infectivity window [i.e. 1989 and earlier].

    b. Any patient known to a Scottish Haemophilia centre who had been tested for HCV and found to be negative [n=76]. This number included mostly infrequently treated patients who had received cryoprecipitate, although some had received factor concentrate. A small number had more severe disease but had received their first treatments between 1987 and 1989. (The relevance of the July 1987 cut off is that that was when PFC changed their virus inactivation procedure to 80C for 72 hrs dry-heat – a procedure which has now been proven to be more efficacious than the previous procedure which was in place until then. Concentrate manufacture by the

old process ceased at this point but small amounts of concentrate already distributed to patients may have been used after this time resulting in a very small number of patients possibly becoming infected in the time frame July 1987 to 1989.

c. Any patient whose sole treatment at a Scottish Haemophilia Centre during the HCV infectivity window was with non plasma based products (e.g. synthetic haemostatic agents such as Desmopressin or Tranexamic Acid), [n=8].

5. This resulted in a list of 460 patients whose first plasma-based treatment, according to the UKHCDO list, was probably or possibly in Scotland.

6. A small number of patients [n=13] known by Scottish Haemophilia Centres to be HCV positive, most likely from treatment in Scotland, did not appear on the list from UKHCDO. Presumably this reflects the potential for the UKHCDO list to have some data missing. This may have arisen as a result of incomplete data collection at the time, errors in transcription into the database or loss of data during recent changes to the database. These 13 patients were then added to the list [giving a final number of 473].

7. These 473 cases were then assigned the centre where HCV was most likely contracted, based on the assumptions made above in relation to site of first treatment. Where the earliest year of treatment included treatments at more than one Scottish centre, the assignment was made arbitrarily. Patients were then designated a unique identifier [Aberdeen A1-A65, Edinburgh E1-E122, Inverness I1-I24, Dundee D1-D34, Glasgow Royal Infirmary G1-G165, Glasgow Yorkhill Y1-Y63].

8. Where the local haemophilia centre had the information, and time permitted, details were added to the table regarding severity of bleeding disorder, HCV antibody status, and current status [dead or alive]. These data remain incomplete and we do not currently have details of causes of death. Filling in these gaps would require a considerable amount of work and would require review of historical medical records which at many centres no longer exist.

9. Classification of patients remaining on the list who never had an HCV antibody test undertaken as 'ever having been diagnosed as NANB hepatitis' or 'not' is difficult, and will require detailed review of historical medical case notes (which in many centres may no longer exist). It is possible that some of these cases never had HCV or NANB. However it is possible that some of these patients have undiagnosed HCV. Therefore it is the intention of the Scottish Haemophilia Centres to, where possible, trace these 'unknowns' and suggest HCV testing where appropriate.

10. Some of these patients only had a very few treatments in Scotland, and were probably visitors who if they did have HCV would likely have contracted it outwith Scotland – but we have insufficient information to be certain.

11. Therefore the final list supplied to PI represents, the estimated maximum number of bleeding disorder patients who contracted HCV from treatment in Scotland. The accuracy of the data are limited by the assumptions made. There are small numbers of patients who received PFC factor VIII before July 1987 who are HCV negative and the numbers of patients infected as a result of cryoprecipitate therapy only are likely to be overstated. – as demonstrated by our findings in 4b above].

12. HCV infected haemophilia patients were informed about the suspected low risk of sexual transmission and that partners should be tested. This testing could be undertaken by the partner's GP, by the Haemophilia Centre or by the Infectious Diseases Unit in Glasgow and Aberdeen. In reality, only a small number of partners attended the Haemophilia Centres for testing [approximately 40 between Edinburgh and Glasgow], and I understand from colleagues that only 1 partner was found to be positive. Since the Haemophilia Centre staff had no direct contact with other partners, nor necessarily knew their identity, we have non information on their HCV status.

Regarding specific issues requested in the Appendix to the Section 21 notice, much of this detail is not yet available. Current summary is as follows:

1. *Number of haemophilia patients treated at the Centre who contracted NANB /HCV.* At present all we can provide is the attached excel spread sheet detailing treatment details of the 473 patients we believe have, or possibly could have contracted HCV from treatment in Scotland. We believe this figure is a cautious overestimate and with time we may be able to identify some of these patients as being HCV negative.

2. *The number of such patients suffering different types of bleeding disorder.* Details of the relevant bleeding disorders are included in the spread sheet.

3. *For each patient dates of first NANB diagnosis and first HCV positive sample.* This information is not currently readily available, and therefore is incomplete in the excel spread sheet. For those patients known to be HCV positive we will be able to identify the date of the first positive test. Since HCV testing was not readily available to Haemophilia Centres until 1991-92, these will be the years of the first positive test for most patients. We do not believe there to have been significant retrospective testing of stored historical samples from these patients (taken prior to 1991). For the very few cases where this may have been undertaken (possibly in Edinburgh, but at the time of preparing this statement we have no certainty of this), there could be an earlier date for first positive HCV test. Dates of first diagnosis of suspected NANB hepatitis will require review of historical medical records. Such records may no longer be available and even if

they are may not yield sufficient details to determine if, and when, the patient was thought to have a diagnosis of NANB. It should be noted that some patients on the list were only treated once or very occasionally in Scotland. These were likely visitors and tracing them now to establish their HCV status may be impossible. In reality of course the date of first suspected NANB or HCV was the date of first receipt of any large pool concentrate.

4. *Types of blood products administered to such patients.* Details are included on the spread sheet as provided to us from UKHCDO. These include treatment by year, product type [including PFC or commercial if known] and location. For the 13 patients added to the list from local centre information, this information is included where available, although in some cases specifics are lacking.

5. *The number of such patients who have died and if HCV was a major contributor to death.* To date we have not been able to establish with certainty the current status {alive or deceased} for many patients on the list. This work is ongoing. We also have no readily available information on causes of death, but again efforts will be made to establish this detail. Thus at present we are unable to offer even an estimate of the numbers requested.

A further document will follow. This is the result of an effort by the Scottish Haemophilia Centres to document key features relating to HCV infection in patients looked after in the Scottish Centres. The patients included were predominantly infected in Scotland but include small numbers of HCV infected patients who had moved to Scotland and were being cared for in a Scottish centre (n=293).

A set of relevant questions, detailed below, were drawn up and agreed upon by the haemophilia directors. Each centre then independently provided the required data on all HCV patients known currently or in the past that could be recalled from centre records where they were available.

The key questions addressed were:

1. The number of patients who had ever been HCV infected (HCV antibody (Ab) positive) as a result of the use of coagulation factor concentrates or cryoprecipitate for the treatment of an inherited bleeding disorder or acquired haemophilia.

2. The number of patients who had spontaneously cleared their HCV infection (HCV Ab positive, PCR negative not as a result of antiviral therapy).
3. The number of patients who had received anti-HCV monotherapy with alpha interferon and the rate of success of the treatment in clearing HCV infection.

4. The number of patients who had received anti-HCV combination therapy with alpha interferon and ribavirin and the rate of success of the treatment.

5. The spread of genotype of HCV in the infected patients.

6. The number of patients who had had liver biopsy and the complication rate.

7. The number of patients who had developed primary hepatocellular carcinoma.

8. The number of patients who had been referred for and had undergone liver transplant.

9. The number of patients alive in July 2007

The data were collected where possible the outcomes in our cohort were compared with historical data on the outcomes for other HCV infected cohorts who had not become HCV infected as a result of treatment with blood product therapy.