Witness Name: Prof Michael Makris
Statement No.: WITN4033023
Exhibits: WITN4033024 - WITN4033025
Dated: 27/11/2023

**INFECTED BLOOD INQUIRY**

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**SECOND WRITTEN STATEMENT OF PROFESSOR MICHAEL MAKRIS**

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I provide this statement in response to a request under Rule 9 Request of the Inquiry Rules 2006 dated 15 November 2023.

I, Professor Michael Makris, will say as follows: -

## Section 1: Introduction

1. My name is Michael Makris, and my date of birth is GRO-C 1959. My professional qualifications are MB BS, MA, MD, FRCP, FRCPath.

2. Details of my employment history, membership of committees/groups/organisations/parties relevant to the Inquiry's Terms of Reference and my involvement in other inquiries, investigations, criminal or civil litigation is laid out in Section 1 of my first witness statement to the Inquiry, **WITN4033001**.

3. Since my previous statement, I have retired from clinical practice. I am now associate editor of the journal Research and Practice in Thrombosis and

Haemostasis, and I am due to take over as Editor in Chief of this journal on 1st January 2024.

**Section 2:**

4. *Please respond to the question laid out under the heading "**Issues to be addressed by your witness statement"** in the Rule 9 request we sent you with this template.*

On 20 October 2023 I posted on X a tweet that said: *"I am hoping that the @bloodinquiry will recommend in their final report that all persons who have been infected with hepatitis C and who cleared it, should get reviewed by a liver specialist at least once. At this review it should be established if long term follow-up and surveillance by the liver team is required. If surveillance is required, there should be a named doctor/team responsible for making sure it takes place on time."*

I have been invited by the Infected Blood Inquiry to expand my thoughts on the above tweet by submitting a supplementary witness statement.

Persons with haemophilia and hepatitis C were treated with various forms of antiviral therapy over a period of more than 35 years. The first patients to receive interferon-based therapy were in 1987 and the latest patients in 2023. Many of the patients, especially prior to the last decade, were treated for hepatitis C through the haemophilia centres, without referral to hepatologists.

As of today, I believe that all persons with an inherited bleeding disorder and active hepatitis C in the UK will have been offered therapy, and I also believe that over 95% will have cleared the hepatitis C virus.

There is an assumption by many infected and affected individuals, as well as general practitioners and haemophilia centre staff that once you clear the hepatitis C infection, you can forget about it. This may be the case for some, but not for a significant number of previously infected persons.

Depending on when a person with an inherited bleeding disorder was treated for their hepatitis C, they will have been infected for anything from between 10 to over 40 years before they cleared the virus. Their infection is likely to have occurred at the time of their first exposure to factor concentrate during the period 1972-1985.

Individuals who cleared the hepatitis C after treatment with the newer antiviral drugs after 2015, will have been infected for a minimum of 30 years before clearance. Chronic hepatitis C can be a progressive disease and the longer the patient has had active hepatitis C, the more likely they are to have advanced fibrosis or cirrhosis.

***The current morbidity of the Milan cohort***

The Angelo Bianchi Bonomi Haemophilia Centre in Milan, Italy is one of the largest Haemophilia centres in Europe and has almost 50 years' history of world leading research in Haemophilia in general, and hepatitis C infection of persons with bleeding disorders in particular.

On the 10th October 2023 they published their latest paper on the issue in the journal Blood Advances (WITN4033024). I believe this is of major importance on how hepatitis C is continuing to impact the haemophilia community. The Italian patients were infected at the same time and with largely the same products as persons in the UK, so the results are directly applicable to the UK situation.

Between November 2020 and July 2022, they prospectively screened 119 persons with haemophilia and who had cleared their hepatitis C, for evidence of ongoing liver disease. The screening involved blood tests, standard liver ultrasound as well as a fibroscan test. Twenty-one patients (18%) had evidence of advanced fibrosis/cirrhosis and 51 (44%) had evidence of fatty infiltration (steatosis) in their liver. Three patients were found to have liver cancer. Ninety-two (77%) of the patients had at least one modifiable risk factor for progressive liver disease (alcohol consumption, type 2 diabetes, high blood pressure, high lipids, overweight/obesity).

***The current morbidity of the Utrecht cohort***

The Van Creveld Kliniek Haemophilia centre in Utrecht, Netherlands is one of the largest Haemophilia centres in the world. They have been following and publishing on a large cohort of Dutch patients infected with hepatitis C. The timing and mode of infection of the Dutch patients was very similar to those in the UK.

In January 2023 they published a paper in the journal Haemophilia. In the paper they describe 199 persons with haemophilia who have cleared the virus after treatment with interferon-based regimens (97 persons) or direct acting antiviral (DAA) drugs (102 persons). At the end of the follow-up period 21% and 42% of the persons respectively, had evidence of advanced fibrosis. They were able to calculate that the risk of liver related complications (mainly hepatocellular carcinoma) was 0.2 per 100 patient years for interferon-based treatments and 1.0 per 100 patient years for DAA based treatments. The reason for the higher disease burden and complication rate in the DAA treated patients is that they were treated after an average of 45 years from infection, whilst the interferon-based regimen patients were treated after an average of 29 years.

A 1.0 per 100 patient year risk is significant because this risk is the annual risk, so over a 10-year period the risk will be 10 per 100 patient years or 10%.

***Why should persons with an inherited bleeding disorder be reviewed by a consultant hepatologist if they have cleared their hepatitis C?***

I believe that individuals who were infected with hepatitis C and who cleared the virus fall into three main groups. Investigation with blood tests, ultrasound scan and fibroscan will result in persons placed in one of three groups.

a) If they have normal liver enzymes and no evidence of fibrosis, they can be reassured that long term follow-up is not required.
b) If they have evidence of advanced fibrosis/cirrhosis they should be entered in a hepatocellular carcinoma screening program, with 6 monthly ultrasound scans, together with regular hepatology follow-up for detection of early liver failure. The chances of success in the treatment of hepatocellular carcinoma depends on how early it is diagnosed, so every attempt should be made for early identification.
c) Persons without advanced fibrosis/cirrhosis but with abnormal liver enzymes should be assessed to find the cause of the abnormal liver enzymes and be given advice on how to change their life/activities to reduce their risk of liver failure.

***Who should the hospital appointment be with?***

I believe all persons with an inherited bleeding disorder who have been infected with hepatitis C infected should have the right to be seen by a **consultant** hepatologist. My concern is that unless this is explicitly stated in a recommendation, it will be devolved to the junior medical staff or specialist nurses. Other members of the hepatology team can see the patients for assessment and organise the initial investigations, but the final appointment when long term decisions are made should be with a consultant hepatologist.

**Statement of Truth**

I believe that the facts stated in this witness statement are true.

Signed: GRO-C

Dated: 27 November 2023

**Table of exhibits:**

| Date | Notes/ Description Exhibit number |
|---|---|
| WITN4033024<br>27/11/2023 | Scientific paper published on 10th October 2023.<br>La Mura V, Bitto N, Capelli C, et al. Residual burden of liver disease after HCV clearance in hemophilia: a word of caution in the era of gene therapy. Blood Advances 2023; 7:5817-5824 |
| WITN4033025<br>27/11/2023 | Scientific paper published in January 2023.<br>Isfordink CJ, van Erpecum KJ, Fischer K, et al. Liver-related complications before and after successful treatment of chronic hepatitis C virus infection in people with inherited bleeding disorders. Haemophilia 2023; 29:106-114 |