



**LETTER OF INSTRUCTION
TO THE CLINICAL GROUP: HEPATITIS
25.09.2019**

Professor Graham Cooke

Dear Professor Cooke,

Re. The Infected Blood Inquiry

1. I am writing on behalf of the Chair to the Infected Blood Inquiry, Sir Brian Langstaff, with instructions for the preparation of a report on hepatitis by members of the clinical group of experts. You have kindly agreed to convene this group for the purpose of this report and to act as a point of contact between the group and the Inquiry. The other members of the group are: **Dr Jane Anderson, Professor David Goldberg, Professor Jurgen Rockstroh, Dr Sara Marshall, Dr Katie Hands, Dr Jonathan Wallis, Professor Philippa Easterbrook, Professor John Dillon, Dr Mallika Sekhar, Professor Mark Thursz, Dr Aileen Marshall, Dr Scott Jamieson, Dr Katie Jeffery, and Dr David Johnston**. I have provided copies of this letter to them. The group is invited to consider which members are best placed to undertake the work outlined below and to notify the Inquiry accordingly.

2. The purpose of the report is to provide evidence about matters within the expertise of the group that may assist the Chair in fulfilling the Inquiry's Terms of Reference. I set out in more detail below the topics and questions that the Chair asks you to address at this stage. The report will be provided to the Core Participants to the Inquiry and will be published on the Inquiry's website. The Chair will ask one or more contributors to the report to speak to its content at the Inquiry's public hearings in late February 2020.
3. In due course, I will ask members of the group, or the group as a whole, to undertake further work to assist the Inquiry. This may include answering questions raised by Core Participants, preparing further reports, conducting discussions with or providing opinions to other expert groups instructed by the Inquiry, giving oral evidence at the Inquiry's public hearings, and carrying out other duties appropriate to the role of an expert to the Inquiry as directed by the Chair through me.

Background

4. As you are aware, the Infected Blood Inquiry has been established to examine the circumstances in which people treated by the National Health Service in the United Kingdom were given infected blood and infected blood products. It is an independent public inquiry under the Inquiries Act 2005 ('the 2005 Act').
5. The provision of such blood and blood products led directly to people becoming infected with hepatitis B virus ('HBV'), hepatitis C virus ('HCV'), human immunodeficiency virus ('HIV') and other diseases. Other people were indirectly infected.
6. The Inquiry's Terms of Reference require it to consider and report upon a wide range of issues. These include:

"To consider the impact of infection from blood or blood products on people who were infected ("those infected") and on partners, children, parents, families, carers and others close to them ("those affected"), including:

- a. *the mental, physical, social, work-related and financial effects of:
 - i. being infected with HIV and/or HCV and/or HBV in consequence of infected blood or infected blood products;
 - ii. the treatments received for those infections.”*

The report, which the group is being asked to produce at this stage, will assist the Chair in considering this part of the Terms of Reference.

- 7. Among the other matters that the Inquiry is required to consider are the following:
 - 7.1. What was, or ought to have been, known at any relevant time about the risks of infection associated with blood donations and blood products.
 - 7.2. The actions of relevant individuals and bodies involved in decision-making in relation to the use of blood and blood-products.
 - 7.3. The nature, adequacy, and timeliness of the response of relevant individuals and bodies to the use of infected blood or infected blood products to treat NHS patients.
 - 7.4. The nature and extent of any attempt to identify those who may have been infected and/or who might benefit from treatment, including the adequacy of any ‘look back’ exercise.
 - 7.5. Whether and to what extent people may have been exposed to the risk of diseases other than HBV, HCV, and HIV as a consequence of the use of infected blood and blood products.
 - 7.6. The identification of any individual responsibilities as well as organisational and systemic failures in relation to any of the matters falling within the Terms of Reference.

It is likely that you will be asked in due course to produce further reports relevant to these matters.

8. A full version of the [Terms of Reference](#) may be found on the Inquiry's website. The website also contains the Inquiry's [List of Issues](#), which provides more detail of the matters that may be explored during the course of the Inquiry.
9. The Inquiry must report its findings to the Minister to the Cabinet Office and make any recommendations as soon as practicable.

Instructions

10. The Inquiry has received and considered many written witness statements from those who have been infected (or whose partners or family members were infected) with hepatitis as a result of receiving infected blood or infected blood products. The Inquiry has also heard a substantial amount of oral evidence from such individuals. So as to inform his analysis and consideration of that evidence, the Chair would be assisted at this stage by receiving a report setting out; the up-to-date clinical knowledge on the different types of viral hepatitis which can be transmitted via blood and/or blood products; the treatments which have been, and those which are now offered to those with hepatitis; and the potential symptoms, side effects and consequences of infection and/or treatment. You will note that some of the questions ask for information about developments and treatments during previous decades. Please answer these questions by reference to what is now known and understood.
11. The Chair is conscious that as members of the clinical group you have great expertise and experience in your respective fields. The topics and questions set out in the paragraphs that follow are intended to provide a focus and structure to your work for the Inquiry. If you feel that the topics or questions could helpfully be rephrased, or if there are matters that you consider should be added or omitted from those set out below, then please provide your suggestions in a letter to me. The Chair will consider any points that you raise and I will respond to you with his decision.

12. Please note that you are not being asked to express an opinion on the circumstances of any particular individual person.
13. For ease of drafting, the questions below do not repeatedly differentiate between different types of hepatitis and generally refer simply to 'hepatitis' or 'blood borne viral hepatitis' rather than, for example, to hepatitis C or hepatitis B. However, the Inquiry expects that your report will differentiate between the different types of hepatitis that can be transmitted via blood and/or blood products, and the different genotypes, in answering these questions. Please also address hepatitis Delta (hepatitis D or HDV) when considering hepatitis B and its complications.
14. The Chair has found chapter two of the Krever Commission report (provided with these instructions) helpful in informing his understanding. The Chair would therefore like to know the extent to which the matters set out there remain accurate so far as they fall within your particular field and to what extent the science has developed.
15. As far as possible, your report should cover the following topics and questions insofar as they are within your areas of expertise and it is possible to address them on the evidence and data available to you.
 - 15.1. An explanation of what hepatitis is.
 - 15.2. An explanation of what the different types and genotypes of blood borne viral hepatitis are.
 - 15.3. A short history of the emergence of blood borne viral hepatitis in the UK and what has been known and understood about the different types of blood borne viral hepatitis from their emergence to the present day.
 - 15.4. Whether the virus causing hepatitis has changed or mutated since its emergence, and if so, how and with what consequences to the disease.

- 15.5. How blood borne viral hepatitis is transmitted. Please explain this in relation to both whole blood and blood products.
- 15.6. How blood borne viral hepatitis is diagnosed, and a summary of how this has changed over the years. Please include descriptions of the procedures used to effect a diagnosis. Please also consider the extent to which testing for hepatitis has become more common over the years and the factors or criteria which a clinician should consider when deciding whether to test.
- 15.7. A description (to the extent that the data is available) of how reliable the various diagnostic tests have been over the years.
- 15.8. A description of the signs and symptoms a person may experience when first infected by a blood borne viral hepatitis and how common these are. Explain how a patient usually presents when first infected and the longevity of any symptoms.
- 15.9. Please note that in some witness statements from those infected this has been described as an acute bout of hepatitis; alternatively, there have been unexplained jaundice and/or abnormal liver function tests and/or other abnormal blood results. In other witness statements there is no recollection of an “acute” phase of hepatitis. Can you explain why there is this difference and whether there is any long term impact on symptomatology and/or prognosis, depending on whether or not there was an acute phase when first infected?
- 15.10. A description of the signs and symptoms – physical, cognitive, and mental – that a person will or may experience when chronically infected with a blood borne viral hepatitis. Please note that the Inquiry has received both written and oral evidence from those who have been diagnosed with hepatitis C and/or hepatitis B, many of whom have reported a range of different chronic symptoms arising from the disease.

Some of the key symptoms that have been described in the statements are listed in Annex 1 to this letter. Please consider this list when addressing this topic.

15.11. A description of:

- (a) The natural history and progression of viral hepatitis, identifying the prognostic factors determining progression to potential complications, the main potential complications, prognosis and life expectancy;
- (b) The treatment options for liver cirrhosis and liver failure and how they have evolved;
- (c) The treatment options for liver cancer and how they have evolved.

15.12. When considering paragraph 16.11. above, please consider in particular:

- (a) Whether the prognosis is different if a person has lived with the disease for many years compared to a person who has been infected in recent years? If so, please explain why and how.
- (b) Whether early diagnosis and/or treatment makes a difference to prognosis? If so, is there is an optimum period of time within which a person should receive treatment? Has this differed over time?
- (c) Whether (and if so why and how) the prognosis is different for a person being exposed to the same type of blood borne viral hepatitis but on more than one occasion from different batches of infected blood or blood products (whether or not this exposure gives rise to infections of different genotypes of hepatitis), as against a person who has been infected on one occasion only?

(d) Whether (and if so why and how) the prognosis is different for a person being exposed to more than one type of blood borne viral hepatitis, as against a person who has only been infected by one type?

(e) Whether (and if so why and how) the prognosis is different for a person who is co-infected with HIV compared to a person infected solely with hepatitis?

15.13. A description of the different treatments that have been provided to those infected with a blood borne viral hepatitis over the years up to the present day. Please set out the requirements of each treatment regime, any contra-indications to the treatments and the known side effects.

15.14. An analysis of:

(a) The predictive factors in establishing the likelihood of specific treatments being successful; and

(b) How effective the various treatments have been over the years for those infected with blood borne viral hepatitis.

15.15. A description as to what is known about the short and long term impact of those treatments on patients. Please note that the Inquiry has received a substantial amount of written and oral evidence from those who have been treated for blood borne viral hepatitis over the years who have reported a range of significant side-effects and symptoms arising from that treatment, many of which have been listed in Annex 2 to this letter. Please consider this list when giving your opinion on this issue, stating whether it is your view that such symptoms or side-effects are likely to be, or may be, attributable to the hepatitis treatment and the likely longevity and severity of any such symptoms or side-effects.

15.16. What is the significance, in terms of symptoms, impact and treatment, of:

(a) co-infection with HIV?

(b) co-infection with a different type of blood borne viral hepatitis?

(c) co-infection with other viruses?

15.17. To what extent, and how, does hepatitis affect people with:

(a) haemophilia,

(b) von Willebrand disease,

(c) thalassaemia,

differently from those who do not have a bleeding or blood disorder?

15.18. Whether, as a result of the treatments currently available, hepatitis can be “cured” or whether it remains dormant and is only “undetectable”.

15.19. Where a patient has “cleared” hepatitis, whether there may remain impacts on the patient’s long term health compared to a person who has not been so infected.

15.20. A description of:

(a) Symptoms of hepatitis a person can suffer after the hepatitis has cleared; and/or

(b) Side effects and/or physical or psychological consequences of treatment after the treatment has concluded?

Please note that the Inquiry has heard and read evidence from individuals whose hepatitis has cleared and who are no longer receiving treatment but who continue to experience similar symptoms to those which they experienced prior to and/or during treatment.

- 15.21. Does being infected with a blood borne hepatitis virus and/or undergoing treatment for it make a person more susceptible to developing other diseases or illnesses? If so please summarise the known and suspected conditions associated with hepatitis and/or its treatment.
- 15.22. The Inquiry has received evidence from witnesses who have suffered from other health conditions or complications which they consider were or may have been caused by their hepatitis infection, alternatively by the treatment which they received for the hepatitis, or at least causally related to the infection or treatment to some extent. These are listed in Annex 3 to this letter. Please state whether you consider that there is or may be a causal link between such conditions and the hepatitis and/or the treatment for hepatitis.
- 15.23. What advice and information would you expect a person now to be given about hepatitis, including advice and information about risks of transmission, prognosis and treatment options?
- 15.24. Following successful treatment, such that the person has achieved a sustained virological response (SVR), what follow up scans, blood tests and/or other checks should the person receive, how often and over what period of time?
- 15.25. Please outline the work being undertaken to find a cure for HBV.
- 15.26. Please outline the WHO initiative to eliminate hepatitis by 2030 and the steps that each country is required to take.

Further evidence

16. If there are issues on which you consider that you require further evidence before being able to reach a conclusion on some of the topics above, then please set them out in the report or in a separate letter to me. Where practicable, the Inquiry will seek to obtain such evidence as you require and provide it to you.
17. Where appropriate, you should provide provisional answers to the questions set out above, qualifying them as necessary with reference to further evidence or research that may be required to provide a more complete answer.
18. The manner in which you address the topics set out is a matter for you, as is the way in which you express your conclusions and any qualifications that accompany them.
19. The report should make clear if there are any matters on which it is not, or may not be, possible to provide an expert opinion, for example due to the lack of available information. The report should give the reasons for any such limitation.
20. If there is a range of professional opinion on a particular issue covered in the report that must be made clear and the range of opinions summarised. The report should explain why you have reached the particular conclusion that you have.
21. If there is a disagreement among group members about any matter within the report, then this too should be made clear. The report should summarise the range of opinions, attribute them to the relevant group members, and provide the reasons explaining the views expressed.
22. The Inquiry will be instructing other expert groups during the course of its work. You may consult freely with members of these other expert groups, as may

help you, but should acknowledge in your report what, if any, material assistance their input has given you.

Expertise and Duties of an Expert

23. If having read this letter you or other members of the group feel that you do not have the appropriate experience or expertise then please let me know immediately. You should also notify me if you have any queries or require any further information.

24. As an expert witness, you have a duty to exercise reasonable skill and care in carrying out your instructions and must comply with any relevant professional code of practice. Your overriding duty is to assist the Inquiry and to provide your unbiased opinion as an independent witness in relation to those matters which are within your expertise.

Format of the Report

25. In preparing your report please make sure that:
 - 25.1. It sets out details of the qualifications of all members of the group contributing to the report and their clinical and/or academic experience.

 - 25.2. It gives details of any literature or other material which you have relied on.

 - 25.3. It contains a statement setting out the substance of all facts and instructions which are material to the opinions expressed.

 - 25.4. It makes clear which of the facts stated are within your knowledge.

 - 25.5. It identifies who carried out any other work used for the report. The report should give the qualifications for the individual and indicate whether their work was carried out under your supervision.

- 25.6. Where there is a range of professional opinion on the matters dealt with in the report, it summarises the range of opinions and gives reasons for the opinion reached.
- 25.7. It contains a summary of your conclusions.
- 25.8. It sets out any qualification to an opinion or conclusion provided.
- 25.9. It contains a statement that each of the contributing group members understands their duty to provide independent evidence and has complied with that duty.
26. The final report must be verified by statements from all group members who have contributed to the report, saying:
- “I confirm that in respect of those parts of this report to which I have contributed:*
- (i) I have made clear which facts and matters referred to in this report are within my knowledge and which are not.*
 - (ii) Those that are within my knowledge I confirm to be true.*
 - (iii) The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.”*
27. You should let me know immediately if at any time after producing your report and before the conclusion of the Inquiry you change your views. It is also important that you notify me promptly if you feel it is necessary to update your report after it has been finalised, for example because new evidence has come to light.
28. The report should be reasonably concise and expressed as far as possible in straightforward language. Where technical or clinical terms are used, and their meaning may not be obvious, please provide a brief explanation as to their meaning.

29. I would be grateful if, in general, Professor Cooke would undertake to be the principal point of contact for all correspondence between the group and the Inquiry.

Timetable

30. I would be grateful if you can provide a draft copy of your report by 31 December 2019. The Inquiry's oral hearings are under way and the Inquiry wishes to hear evidence arising from the report in oral hearings in late February 2020.
31. I ask for the report to be provided in draft in the first instance so that I can approve its format, check that the formal requirements for an expert report mentioned above are fulfilled correctly and ask for any queries to be addressed before the report is signed.
32. Once the report is finalised, a copy will be disclosed to the Core Participants and will be published on the Inquiry website. It may be that once Core Participants have reviewed this letter of instruction or your report they will identify further issues that I may wish to raise with you.
33. One or more group members will be asked to attend the Inquiry to give oral evidence in late February 2020.
34. I may also provide you with further instructions at a later date in respect of other matters on which we seek evidence from the group.

Fees

35. I will correspond with you separately about arrangements for your fees.

Next Steps

36. To progress matters as quickly and efficiently as possible, I would be grateful if you and the other group members can return to me a signed confidentiality undertaking, if you have not already done so.
37. As I have indicated in this letter, and if you feel that it is appropriate, please write to me if you consider that the questions or topics should be amended or changed.
38. May I thank you and the other group members once again for agreeing in principle to assist the Inquiry. If there is anything that I can do to assist or there are any aspects of these instructions that you would like to clarify then please do not hesitate to contact me.

Yours sincerely,



Moore Flannery
Infected Blood Inquiry, Secretariat



ANNEX 1: EXAMPLES OF SYMPTOMS DESCRIBED IN WITNESS STATEMENTS¹

- Cognitive difficulties, often described as “brain fog”, including lack of concentration, memory loss, verbal processing difficulties and confusion
- Mood disturbances including depression, anhedonia, anxiety, mood swings, bruxism, and seasonal adjustment disorder
- Sleep disturbances including insomnia, tiredness and extreme fatigue
- Spells of dizziness
- High blood pressure
- Sweating and or difficulties regulating body temperature
- Jaundice
- Joint pain and or inflammation in the joints; cramps in particular joints, or the whole body locking up
- Paraesthesia

¹Please note that some witnesses describing these symptoms may be co-infected with HIV and HCV and/or HBV.

- Clubbing of fingers and toes
- Digestive problems including irritable bowel syndrome, nausea and vomiting, reflux and bloating
- Issues with weight gain and/or unexplained weight loss
- Lipodystrophy and / or lipoatrophy
- Strong urges to eat sugary foods
- Anal bleeding
- Aching in liver area
- Suppressed immune system resulting in frequent colds, flu and other infections
- Unexplained fevers
- Cystitis
- Thrush
- Headaches
- Sores and blistering, described as stress related by some witnesses; others simply as weeping sores
- Other skin symptoms including severe itching and dry lips
- Hair loss
- Inability to produce breast milk

ANNEX 2: EXAMPLES OF SIDE EFFECTS OF TREATMENT DESCRIBED IN WITNESS STATEMENTS

- Mood and or cognitive disorders including suicidal thoughts, depression, personality changes including extreme agitation and aggression, moodiness, anger, irritability, confusion and feeling lost, psychosis, loss of libido, nightmares, insomnia
- Digestive difficulties including; vomiting, severe cramps, nausea, upset stomach, severe loss of appetite, intolerance to certain foods
- High fever and flu like symptoms
- Difficulties regulating temperature including hot and cold sweats
- Septicaemia
- Poor circulation
- Bleeding issues including increased vaginal bleeding, severe nose bleeds, anaemia, and bruising
- High blood pressure
- Cardiac arrhythmia
- Hypothyroidism
- Fatigue
- Headaches and dizziness
- Deafness

- Joint pains and/or aggravation of arthritis
- Skin conditions including painful rashes, blistering and peeling skin, highly itchy skin, dry skin, psoriasis
- Light sensitivity
- Exacerbation of arthritis
- Hair loss
- Mouth ulcers
- Thrush
- Visual problems including sties, blurred vision
- Erectile dysfunction
- Persistent cough
- Chronic breathing problems including pulmonary fibrosis
- Asthma
- Mobility difficulties with poor mobility and/or losing the use of one's legs

ANNEX 3: HEALTH COMPLICATIONS DESCRIBED IN WITNESS STATEMENTS

- Cognitive issues including on-going brain fog
- Mental health conditions including depression, anxiety, drug and alcohol dependency
- Bi-polar affective disorder
- Stress related skin conditions
- Rosacea
- Actinic purpura
- Osteopenia
- Osteoporosis
- Arthritis including rheumatoid arthritis and polyarthritis
- Fibromyalgia
- Periodontitis
- Carpal tunnel syndrome
- Spinal stenosis
- Sacralagenesis
- Systemic lupus Erythematosus

- Hughes Syndrome or Antiphospholipid Syndrome
- Type 111 cryoglobulinemia
- Hypertension
- Transient ischaemic attacks
- Heart disease
- Raynaud's syndrome
- Thrombocytopenia causing bruising and/or extensive nose and other bleeds
- Cerebral haemorrhage
- Variceal bleeds
- Encephalopathy
- Parkinson's disease
- Bouts of Bell's palsy
- Vascular dementia
- Epilepsy
- Asthma
- Sleep apnoea
- Sarcoidosis

- Pulmonary emboli
- Chronic lung disease
- Bronchiectasis
- Bowel problems including irritable bowel syndrome
- Bladder problems including bladder erosion and incontinence
- Pancreatitis
- Bile duct blockages
- Diabetes
- Enlarged spleen
- Gall stones
- Thyroid problems
- Umbilical hernia
- Glomerulonephritis
- Kidney failure
- Hypogonadism
- Difficulties in conceiving
- Polycystic ovarian syndrome

- Eye problems including early cataracts and glaucoma
- Cancer including liver cancer, ovarian cancer, lung cancer, breast cancer, bowel cancer, skin cancer and non-Hodgkin's lymphoma
- Increased susceptibility to viruses and infections
- Regular bouts of shingles
- Glandular fever