Friday, 28th February 2020

(10.30 am)

SIR BRIAN LANGSTAFF: Today, the last day of this week of largely expert testimony, we have another first for those of us in the Inquiry from abroad, we have Professor Rockstroh joining us from Germany.

Professor Rockstroh, can you hear me?

PROFESSOR ROCKSTROH: Yes, I can hear you very well.

SIR BRIAN LANGSTAFF: Thank you.

What we're going to do is start off by swearing in the other experts on the panel and then Mary, my clerk, will swear you in, take an affirmation from you, and then you'll be asked questions by counsel to the Inquiry.

Thank you very much for joining us and making the time. We understand you have an hour, and I'm delighted to have been able to take advantage of you for that period of time at least. So thank you very much in anticipation. May the experts be sworn.

MALIKA SEKHAR (affirmed)

PROFESSOR DAVID EDGAR (affirmed)

DR SARA MARSHAL (affirmed)

DR RICHARD GOODING (sworn)

DR KATE RYAN (affirmed)

DR OLIVER TUNSTALL (affirmed)

PROFESSOR JÜRGEN ROCKSTROH (affirmed)

SIR BRIAN LANGSTAFF: Thank you very much.

MS RICHARDS: Sir, before I ask the experts to introduce themselves and say a little bit themselves, I wanted to say a couple of words about the nature of the evidence we'll hear this morning and the kind of material we won't be looking at this morning.

So the evidence will be following a very similar format to the evidence we've heard over the last four days, but with a slightly different focus. Whereas the focus of the last four days has been looking at impact in medical and psychosocial terms of the infections, today we're considering some of the underlying disorders or conditions which gave rise to the receipt or administration of treatment, whether by way of blood products or blood for those conditions.

And as a result, the report that we have falls essentially into three parts, and our different members of the panel are likely to be dealing with different parts. So the first part

looks at bleeding disorders, treated, as we know, with blood products, particularly factor concentrates.

The second part of the report deals with certain inherited disorders of haemoglobin for which regular blood transfusion was a mainstay of treatment. And then the third part of the report looks at primary immunodeficiency disorders for which immunoglobulin replacement therapy was a mainstay of treatment, and so that's why there are a number of different focuses of the evidence today.

In common with the approach taken to experts earlier in the week, we will not be asking questions about the correctness or otherwise of treatment decisions that may have been taken in relation to any of those disorders.

So whilst the reports do have, and this report does have, a section looking at treatment for bleeding disorders in particular pre-1970 and post-1970, I'm going to be asking very little about that, and I've explained that to colleagues behind. The reason for that is threefold: firstly, as the panel members have made clear to the Inquiry, they were not, in

relation to bleeding disorders, clinicians practising in the 1970s and 1980s, so they don't have direct firsthand knowledge to draw on in that respect.

Secondly, as a result, when they've sought to give us an overview of the picture in relation to the historic period, they have quite properly drawn on publicly available sources, which has inevitable limitations because the Inquiry has available to it far greater amounts of contemporaneous material, and we couldn't possibly ask clinicians to take time out of their full time clinical practice to look through the thousands and thousands of documents that we have relating to decisions in the 1970s and 1980s. And the third reason is that ultimately, of course, these are the questions of fact that go to the heart of issues at the Inquiry that are for you, sir, to determine.

That's a long way of explaining that the focus of my questions today, as with the questions earlier this week, will be on what is currently known and understood about the relevant disorders.

So after that introduction, can I ask each

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member of the panel to just introduce themselves and say a couple of sentences about their area of expertise.

I'll start with you, please.

DR SEKHAR: I'm a consultant haematologist at the Royal Free Hospital and University College Hospital, and this has been since 2011. I qualified in 1982 and came to England in '87. I had then worked for a bit as a registrar trainee and then became a consultant in '95.

My main responsibilities are, at the present time, to look after some patients -- some categories of patients with certain types of blood cancers, and to be the lead for the Blood Transfusion Service at the two hospitals I work in.

MS RICHARDS: Professor?

PROFESSOR EDGAR: My name is David Edgar, I'm a consultant immunologist. I qualified in medicine in 1995 and I was appointed consultant in Belfast in -- sorry, in 1985 and I was appointed consultant in Belfast in 1996.

Over the last year I've been working in Saint James's Hospital in Dublin, and my main interest relevant to this Inquiry is looking

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after patients with primary immunodeficiencies who would receive immunoglobulin replacement, but I also run a laboratory service and also an allergy service.

DR MARSHALL: My name is Sara Marshall and I'm a consultant clinical immunologist and for the last 35 years I've been involved in the care of patients with immune problems, both immune deficiencies and autoimmune diseases. I've also had a research career and I currently work for a research charity called the Wellcome Trust, where I am head of clinical research.

DR GOODING: My name is Richard Gooding. I'm a consultant haematologist working in Leicester, and I qualified in 2003 and became a consultant in 2012. I'm currently the Haemophilia Centre director of the Comprehensive Care Centre in Leicester, and my special area -- my areas of special interest are haemophilia and I manage both adult and paediatric patients with bleeding disorders, and I also manage patients with thrombotic disorders and manage anti-coagulation.

DR RYAN: Good morning, my name is Kate Ryan. I'm presently a consultant haematologist in

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Manchester. I qualified in 1981 and trained in London before becoming a consultant in West London in 1994, moved to Manchester in 2011. I have been looking -- my specialist interest is inherited haemoglobinopathy, so sickle cell, thalassaemia and other rare inherited anaemias, and I have about 30 years' experience of managing these conditions.

DR TUNSTALL: My name is Oliver Tunstall. I'm a consultant paediatric haematologist in Bristol Royal Hospital for Children. I qualified in '96 and have been a consultant since 2010. I run the Paediatric Haemophilia Service and the South-west Paediatric Haemophilia Network. As well as managing children's bleeding disorders, I also manage other blood disorders in children.

MS RICHARDS: Professor Rockstroh.

PROFESSOR ROCKSTROH: Yes. So I was qualified in 1989 at the -- and I started working at the department of medicine, University Hospital in Bonn, where I did my internal medicine and infectious diseases training and became a consultant of infectious diseases in 1998. The story is that in Bonn we have the very large cohort of haemophiliacs, 420, so it's the

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largest existing cohort with HIV infection, was treated in our HIV clinic, and that's where I spent my clinical work -- did my clinical work, and also my research, which has been mostly around HIV and hepatitis co-infection, in the last 30 years.

MS RICHARDS: Thank you.

Professor Rockstroh, as we only have you for a limited period of time I'm going to start with questions I think you're probably best able to help us with, which is looking at the implications of HIV and hepatitis co-infection, in -- specifically for those who have a bleeding disorder.

Can I ask you, first, to concentrate on the position of individuals with a bleeding disorder who are infected with HIV. That's my first set of questions.

PROFESSOR ROCKSTROH: Yes.

MS RICHARDS: Can I just ask, first of all, are there any studies or research that you're aware of that focus on HIV in what I might call the wider infected blood community? So looking at those who were infected as a result of treatment for bleeding disorders, but also partners who

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may have become infected and the broader family position. Do you know of any research or studies in that field?

PROFESSOR ROCKSTROH: Yes, so we obviously analyse our own cohort of infected haemophiliacs, so then there's a limitation that it's mostly haemophiliacs. We have some von Willebrand's but not -- but at least numerically that's much lower, and we also looked at their partners.

We had -- 10% of the female partners got HIV infected, and we have a paper published on that. The overall course of HIV in haemophiliacs or other bleeding disorders is not too much different from other patients who acquire HIV. So, in my analysis -- because that's what I did my research on -- it looked as if the outcome was maybe a little bit more favourable in haemophiliacs, mostly based on the fact that they do not develop Kaposi's sarcoma, which was very prominent in gay men, and also if it became pulmonary or, you know, manifestations in the (inaudible) bleeding events and chemotherapy was difficult with advanced immunodeficiency KS to varied terms, and that may have contributed to some of those people dying from KS. In the

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setting of IV drug users, you obviously have a high rate of suicide and overdosing so that had a little impact on their overall survival, but in general terms speaking, the overall average time in untreated HIV was around 10 years, and after an AIDS defining event was 2 years. So -- and that honestly all changed with the advent of antiviral therapy, but really the overall figures are very comparable to other groups.

MS RICHARDS: I think you've identified in the report, because you contribute also to the hepatitis and HIV reports, you've identified I think one particular impact that HIV may have on a person with a bleeding disorder which is that it can cause thrombocytopenia which may increase the bleeding risks; is that right?

PROFESSOR ROCKSTROH: Yes, in consideration of the increased bleeding risks overall in the setting of a bleeding disorder, I listed that because it's the only HIV-associated manifestation which could have an impact, I think it's fair to say, though that mostly patients with low clot, which is a common finding in untreated HIV infection, didn't really lead to a lot of bleeding

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episodes. But I have to say that in the context of hepatitis C, you can also develop thrombocytopenia which is a sign of advanced liver (unclear) cirrhosis. If you HIV and hepatitis C and you had, sort of thrombocytopenia which was enhanced in the setting of cirrhosis that could have actually had an impact and indeed was more likely to lead to bleeding events. Obviously that also plays a role in the setting of advanced liver disease when you have varices and can die from (inaudible).

MS RICHARDS: I'll come on to hepatitis C for a moment but just sticking with HIV and bleeding disorders, treatment for HIV have there been any particular adverse impacts from HIV treatment? Obviously we know there are lots of adverse impacts from the treatment itself but specifically on a bleeding disorder. You've identified in the reports some reports of increased bleeding episodes under commonly used first generation protease inhibitors, I think.

PROFESSOR ROCKSTROH: Yes. So there was in particular a German group in Munster which reported an increased bleeding frequency in

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haemophiliacs receiving first generation protease inhibitors for HIV therapy. This was not really reproduced in our cohort but I have to say our haemophilia treatments had different substitution policy which was always leaning towards the preventive substitution; daily administration of factor, units to prevent any kind of bleeding episode which may have covered this increased risk. So if you are in a centre with a strategy which was less frequent in administration of blood factors, then that might have been true, and we would have covered it in our cohorts. There are reports in literature which do suggest there may have been a higher bleeding episode risk under HIV protease inhibitors.

MS RICHARDS: Looking at it the other way round, you touched on this already, but the impact of bleeding disorder on the progression or severity of HIV or treatment for HIV, you've identified in your report obviously what you describe as profound and multi-factorial impacts of HIV on this cohort but from a clinical perspective (and leaving aside Kaposi's sarcoma which you've addressed separately), as I understand your

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report, the clinical course of HIV or AIDS is not materially affected usually by the cause of transmission, the transmission risk group that the individual fell within.

PROFESSOR ROCKSTROH: Correct. I mean, obviously it is -- all the differences you see between the different key populations really comes from lifestyle, right. In the drug users you have all these additional aspects. You consider the haemophiliacs were, you know, more likely to be into therapy, and come for visits and so forth. So that's maybe why they have just a little bit of a better outcome compared to IV drug users. But otherwise I think there is really no difference. It was the same natural course.

MS RICHARDS: You've identified in your report that one factor that seems to make a significant influence on survival rates was age at time of HIV seroconversion; is that right? Is it understood why --

PROFESSOR ROCKSTROH: That's correct.

Well, I think we have to appreciate that with age you also have changes in your immune system, so in general you would think that someone who is aging that probably a loss of C4

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count would be more meaningful because per se in the setting of age-associated immunodeficiency you would be more likely to be prone for infections. So bacterial infections may be more prominent and so forth. I would say, yes, age is a big player in that setting.

MS RICHARDS: Were there any treatments for AIDS-defining conditions that wouldn't have been available to those with bleeding disorders?

PROFESSOR ROCKSTROH: Let me think. So the majority of patients I saw first developed usually fungal disease, so they had oral thrush and then oesophageal candidiasis, and that could be treated equally well. There's always the limitation that patients with haemophilia or other bleeding disorders had hepatitis C, so the risk of hepatitis toxicity is clearly enhanced in this patient population. So that would be one limitation. Obviously in this setting of liver cirrhosis, if you treat tuberculosis or other things where you bleed a lot, there are toxic drugs that could have had an impact on the dosage or the duration of your therapies because of side effects, but in general you can use the same drugs.

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MS RICHARDS: Then in relation to hepatitis C, can I ask similar questions. What impact does hepatitis C have on a person with a bleeding disorder or for treatment for their bleeding disorder?

PROFESSOR ROCKSTROH: Yes, I think it doesn't really have an impact on the treatment of the bleeding disorder, but obviously the liver disease can eventually move on to liver probiosis, cirrhosis and bleeding complications like resal(?) bleeding and that can obviously be enhanced in the setting of a bleeding disorder.

MS RICHARDS: For hepatitis C, are there any particular issues in relation to treatment for hepatitis C? We've heard a lot about the side effects and adverse events associated with the interferon in treatments, but were there specific problems for those with bleeding disorder either in terms of impact, different side effects, or resistance to treatment?

PROFESSOR ROCKSTROH: I think, in general, because most of the haemophiliacs had a genotype 1A infection, that seemed to respond less favourably than some of the genotype infections. So I think the prevalence of more advanced liver

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disease was higher, the unfavourable genotype, and so overall if you look at the treatment outcome of interferon-based regimens in haemophiliacs always intended to be somewhat lower. Now, unfortunately that has all disappeared in the DAA, where everyone is responding so well, but clearly treatment for haemophiliacs in the early days was relatively challenging with regard to the outcome, which always tended to be a little poorer, and so a lot of haemophiliacs were not willing to undergo this intervention because of the low promise of cure following this intervention.

MS RICHARDS: Are there any studies or research that you can direct us to looking at life expectancy for those with bleeding disorders infected with HIV, hepatitis C, or both?

PROFESSOR ROCKSTROH: Yes. Well --

MS RICHARDS: I'm not necessarily asking for a list now but if you can tell us what you know and we may ask you to supply more details in writing.

PROFESSOR ROCKSTROH: Yes, so obviously the -- so the life expectancy is affected by all of these concomitant diseases, so even in the setting of having just hepatitis C you still have a higher

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risk of developing liver cirrhosis and hepatic carcinoma, and dying from these complications, so that's still much higher, so that impacts obviously your overall survival.

In the setting of HIV, you obviously have a diminished survival with regards to the old days, where we didn't have any anti-viral regimens. And then I think what is particularly important in the context of HIV and hepatitis co-infection, because obviously most of the patients had hepatitis C, so if you had HIV you're likely to have -- having hepatitis C, the risk was very, very high, then you had an even -- much more increased risk of dying from liver disease. And that was particularly true if you belonged to those people who started to develop more (inaudible) immunodeficiency. So the more CD4 count you lost, the higher your risk of dying from liver disease. And that has been also the reason why there were particularly -- guidance in the -- European treatment guidelines for people with co-infection to start HIV therapy earlier to prevent the CD4 count loss which then triggered the faster fibrosis progression in these

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patients.

Then the patients who had, beyond HIV and hepatitis C, also additional hepatitis B infection, was also associated with a more unfavourable outcome. Then there were patients with hepatitis B, C and D. And just to underline the significance of these viral interactions, of all the haemophiliacs we had, every patient with hepatitis B, C, and D and HIV died prior to the advent of highly successful antiviral therapy, because the outcome of liver disease was the worst, and the patients all died prior to the onset of having these regimens available.

So that's really the worst outcome altogether but clearly liver disease has been the main issue in the station(?) population for all the different viral infections.

MS RICHARDS: And there is faster liver disease progression, faster progression to fibrosis and beyond, in co-infected patients?

PROFESSOR ROCKSTROH: Yeah, and so -- and we were one of the first groups to examine that because we saw patients turn yellow, basically, really, in clinic. At first I thought it might be

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related to the anti-retroviral drugs we were using, different elimination and potential accumulation of toxicities in patients who were cirrhotic, but then it really turned out that in the setting of low CD4 counts, patients had an accelerated fibrosis (inaudible) compared to stable CD4 counts, stable-wise haemophiliacs with those who had (inaudible) immunodeficiency and really saw that that was the group where we saw a lot of people dying from liver disease. So we could clearly establish that.

I think one of the interesting questions was: is this reversible if you start giving HIV therapy and have an increase in CD4 count? And there are big cohorts from the United States looking at that and showing that even with the setting up -- giving antiviral therapy, you probably still have a somewhat faster fibrosis progression. So unfortunately HIV does take an impact on the negative side there.

MS RICHARDS: Then can I ask about a different way in which there may have been a burden or impact for those with bleeding disorders infected with HIV and/or hepatitis C, and that's the burden of treatment. These are individuals who

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will already be having to, particularly if they have a severe bleeding disorder, have a substantial amount of treatment. Add to that the burden of treatment for HIV, and we heard a lot of evidence yesterday about how problematic the HIV treatments were in the early decade, and then add to that the burden of the interferon era treatment. Is that something that you observed in your clinical practice?

PROFESSOR ROCKSTROH: Yeah, absolutely. I think there are even some things to add because, first of all, not only do you have, you know, all these issues with the various drug treatments for different diseases, but in the setting of co-infection we also recommended longer interferon durations, which were very burdensome for the patients to tolerate, and unfortunately because the infections were acquired so early -- which means that a lot of the patients had to start early HIV drugs, with a lot of side effects.

So if you look at patients today, when they start anti-retroviral treatment, it's really different because the amount of patients discontinuing therapy because of side effects is

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so much lower than what we had in the old days. A lot of the drugs we were giving for treatment of HIV, those interfered with the hepatitis drugs, right? So ribavirin was not combining with all drugs, it was more anaemia if you had AZT on board, they needed transfusions. So it was really quite an augmented and enhanced toxicity profile in this mix of old HIV drugs in combination with interferon and ribavirin. But even when DAAs became available initially, because of the fact that they had acquired a lot of resistance on other failing HIV regimens, there was a need for trying to find -- how we can find DAAs which are combinable, because of a lot of drug interactions between HIV drugs and hepatitis C drugs, that's what's all disappeared in more recent years with the broader access of different regimens we now have for treatment. But in the early days, treatment in this particular group was actually quite challenging because of the high amount of drug interaction, the presence of HIV drug resistance from earlier non-suppressive regimens which were used obviously in a patient population with a very long duration of HIV infection.

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MS RICHARDS: And presumably one might add to that somewhat complex picture, not just the treatment for the bleeding disorder, the hepatitis, the HIV, but the potential regimes of treatment that an individual might undergo for -- to deal with the side effects of treatment, the AIDS-defining conditions that might have been developed --

PROFESSOR ROCKSTROH: Yeah.

MS RICHARDS: -- the psychological and mental effects of everything that individuals were undergoing. So there may have been a multiplicity of treatments.

PROFESSOR ROCKSTROH: Absolutely.

MS RICHARDS: Do you know whether there were specific contraindications for different treatments or particular problems experienced by this cohort in terms of receiving treatment for the wide range of side effects and other consequences they might have been experiencing? It's a long way of putting a question.

PROFESSOR ROCKSTROH: Well -- yes, well, there were some contraindications coming from drug-related interactions, and so in the end you had to look at every patient and see what was -- because

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obviously you don't want to let HIV replicate. So HIV control is your first absolute must. And then you have to see with which drugs is that possible, and does that allow co-administration with some of the other drugs, or is this going to lead to enhanced toxicity, and do you have to, I don't know, give EPO(?) or transfusions to compensate certain enhanced toxicities? So there were clearly special aspects around drug-drug combinations.

I wouldn't say that there was any real contraindication in general, other than that obviously the setting of cirrhosis you also have contraindications for -- so you can treat with somebody with decompensated cirrhosis, for example, in the interferon, and you can't treat someone with decompensated cirrhosis with most of the DAAs because they're not licensed for more advanced child stages. So there are some limitations reflecting on liver disease stage and drug interactions.

MS RICHARDS: Professor Rockstroh, thank you. I'm going turn to some more general questions about bleeding disorders, which will be directed at the panel sitting here. But

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please do, in the time you have with us, I think we've got you for another 25 minutes or so on the line before you have other clinical commitments, please do join in, contribute, add to anything that's being said by your colleagues.

DR SEKHAR: Could I just make a couple of comments?

MS RICHARDS: Yes, of course.

DR SEKHAR: One is about platelets. So thrombocytopenia was a problem, and is a problem, in this group of patients. One of the things we learned through the early nineties was treating the HIV can improve the thrombocytopenia, and so we became more and more confident about treating thrombocytopenia in the HIV patient cohort.

The second thing is that in the last 10 years or so, treating thrombocytopenia has become more easy and this is especially with relevance to the hepatitis C group of patients and there are new drugs introduced and clinical trials done. So again, treating thrombocytopenia has become easy. It still is a problem but it's now possible to treat them such that it doesn't interfere with other

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things.
MS RICHARDS: Thank you.
DR SEKHAR: The second point is about biopsies in patients with bleeding disorders who might have, say, AIDS-related lymph node enlargements. It was not easy to do that because they were having a bleeding problem but it was also very difficult in the initial stages to have proper correct types of diagnosis because people didn't know, histopathologists didn't know, how to interpret what they were seeing under the microscope. So it took a while before they could distinguish it from cancers and just HIV-related changes.
MS RICHARDS: Thank you.
So I'm going to turn to the first part of the report, and ask questions about what's currently known about some of the key bleeding disorders, and what the current treatment regimes are for them.
I'm going start with haemophilia A, and ask a member of the panel (perhaps Dr Gooding and Dr Tunstall) to tell us first of all, what is haemophilia A? I'm conscious that many people here will have a much greater knowledge about

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any of us about that, but part of our purpose in asking these questions is wider public education.
DR GOODING: Haemophilia A is a bleeding disorder obviously, characterised by reduction of one of the clotting factors, Factor VIII. It ranges in severity from a very mild condition to potentially very severe and it's characterised by bleeding into, typically, muscles and joints. The bleeding severity tends to correlate quite well with the levels of Factor VIII that are detectable in the bloodstream. So a very significant reduction, so typically between 1 and 3 per cent is characterised by a severe bleeding tendency.
We can see essentially what we call spontaneous bleeding but it's essentially driven by normal activities. It's not truly spontaneous. We don't see it in very young infants until they start walking, usually. It's that sort of level of very mild trauma within, say, joints and muscles that can lead to this sort of what we call spontaneous bleeding. Then that can lead to, well, obviously the acute problem, so that sort of pain, discomfort,

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reduced mobility, and that sort of thing and then much longer term problems with joint damage.
MS RICHARDS: Haemophilia A mostly affects males. I'm going to come on to the questions specifically about how it affects females later.
(Witness nodded)
Do you know approximately how many people with haemophilia A there are currently in the United Kingdom?
DR GOODING: I haven't got that statistic with me, actually. It's part of the UKHCDO statistics but I don't have that with me off the top of my head.
MS RICHARDS: Don't worry. We can extract that from the national reports.
DR TUNSTALL: Yes, it's in the thousands.
DR GOODING: Yes.
MS RICHARDS: In terms of what causes haemophilia A or how people may come to have haemophilia A, it's an inherited condition, but not for everybody. There are some for whom it occurs spontaneously through genetic mutation with no family history; is that right?
DR GOODING: Yes. I suppose if you're looking at it

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in terms of inherited and not inherited, there's the more common inherited form in which there's a problem with the X chromosome and that can either be inherited, you know, as in predictably through a family, so there's a known diagnosis, but it can occur with a spontaneous mutation as well and that's about 50 per cent of cases that are seen in that way. So that's all inherited.
There is an acquired form of haemophilia as well which is an autoimmune disorder which is typically seen in older adults. That's an autoimmune condition, so that's very different. So in that individual, they will have had normal levels of Factor VIII and then an antibody will have been produced which will reduce the effectiveness or the levels of Factor VIII. So those are the sort of differences there.
DR TUNSTALL: Sorry, can I just -- we do use the term "inherited" in a slightly confusing way, I think, in that "inherited" is often used as synonymous with congenital with birth or genetic in that sense. So even cases where there haven't been recognised cases of haemophilia in the family, we would still consider it an inherited bleeding disorder, because it's --

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MS RICHARDS: Because it's not acquired in the way that's just been described?

DR TUNSTALL: As opposed to acquired, yes.

MS RICHARDS: In terms of diagnosis with haemophilia A, as I understand it from the report, there may be what you call targeted testing of a baby because there's a known history of haemophilia A in the family, or there may be children who present with symptoms, bruising, bleeding without a family history; is that right?

DR TUNSTALL: So that's right. So if we're aware of haemophilia in the family and we are aware that a pregnant woman is known to carry -- have one copy of the affected Factor VIII gene, then they typically should be referred to see a haematologist during the pregnancy and then plans can be made.

There are various choices about when testing can be done. So there's the option of antenatal testing, antenatal genetic testing of the foetus, or plans can be put in place to test a newborn baby immediately which is usually done on cord blood.

Then there are the cases that come to light for other reasons, typically for severe

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haemophilia that's very early on in life, that they're noticed to have (bruising or bleeding within the first year or two of life) and then typical investigations, the basic screening clotting screens are usually grossly abnormal, and hopefully somebody puts two and two together and the more specialised testing is done and they're referred to a specialist team.

MS RICHARDS: In terms of that specialised testing, you've identified two sets of tests, something called APTT and then factor assays. I wondered if you could briefly explain what those are for us.

DR TUNSTALL: They're tests that are done very commonly in a hospital, something called a coagulation screen or a clotting screen which consists of tests where basically blood is spun into its cellular component in the plasma and the plasma (which is the liquid component of blood) is then tested with activators to see how quickly it forms a blood clot. You can use different activators and they give rise to the PT and the APTT. Those timings are, to a certain extent, predictive of levels of the soluble clotting factors such as Factor VIII.

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In haemophilia A, one would expect a very prolonged APTT, certainly in severe haemophilia A, than an extremely prolonged APTT and then that would lead hopefully in the clinical context to more specialised testing of the Factor VIII activity within the blood.

MS RICHARDS: Then we have as we've heard -- and indeed we've heard from a lot of the evidence we've heard from individuals -- the classification of haemophilia A into severe to moderate and mild. I think you've touched on the levels that would identify severe haemophilia. Could you just talk us through the different levels of Factor VIII that would lead to someone being classed as mild, moderate, and severe?

DR GOODING: Typically, the classification would be that severe patients would have less than 1 per cent Factor VIII levels, moderate patients would be between 1 and 5, and then mild would be 5 up to perhaps 30 or to the lower limit of normal. So that's the classification. Although, there is -- I mean, as with anything in life, you know, it's a description of a more complex sort of system, really. So there are

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other factors that can lead to bleeding and so there is some, whilst that's a -- there is good correlation and that's a NICE classification, then there may be people who, for one reason or another, may have a more severe phenotype and more severe sort of expression even though their levels are slightly higher, or who conversely might be seen to be relatively protected for other reasons, even though the levels of Factor VIII are low.

So it's not an absolute but it's probably the best description that we've got, really.

MS RICHARDS: I wasn't going to ask you anything historical so please tell me if you can't answer this, but are those levels ones that have been, as far as you know, fixed in clinical practice for a significant period of time or have there been a number of changes over the years?

DR GOODING: They're pretty fixed, aren't they?

DR TUNSTALL: I believe in the UK we often use less than 2 as severe rather than less than 1.

Then there was an attempt standardise things internationally which use less than 1. There's actually a sort of growing movement as the evolution -- there are practical implications

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for how one recommends treatment in haemophilia depending on those levels and depending on that classification. There is a certain amount of questioning as whether we should consider severe as in particularly those children who are likely develop spontaneous bleeds, and develop joint problems, and should be considered for regular preventative treatment as severe, maybe more -- less than 3. But for now, formally, we use less than 1, 1 to 5, and greater than 5.

SIR BRIAN LANGSTAFF: Before you go on, the percentage is obviously a percentage of something. It would imply 100 per cent, so 1 per cent is 100th of that, but what is 100 per cent? I understand that's not, as it were, the most you can get. That's normal, is it?

DR TUNSTALL: 100 per cent is based on if you measure 100 or 1,000 people without haemophilia, and you draw Factor VIII and you get a nice normal curve, then 100 is based on the average level.

SIR BRIAN LANGSTAFF: The average or the median?

DR TUNSTALL: Well, the average (which is pretty much the median, I think, in these cases) and

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then normal range is considered approximately 50 to 150. So it's the machines are calibrated to that standardised setting.

SIR BRIAN LANGSTAFF: Arising out of counsel's last question to you, has the sense of what 100 per cent is or the normal (50 to 150 per cent) is, has that changed over time or has that been broadly consistent in terms of international units?

DR TUNSTALL: I couldn't say whether it's shifted at all. I suspect it's shifted a little bit and there are efforts to standardise these things so we establish international units, so rather than per cent. Per cent is what we often use, and it's well understood, and easy to talk about. We often use -- there's an equivalent measure which is international units per decilitre which gives the same numbers. There are efforts internationally to set that standard.

I don't know to what extent that shifted, but in some ways the normal levels are less important than the bottom end because the difference between having levels of 95 or 100 is insignificant, while the difference between having 1 or 2 can be very significant.

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DR GOODING: It is an important point, though actually, mentioning percentage because it does sound confusing because to have 50 per cent being normal just sounds strange. But it is just the terminology that's used. So yes, 100 per cent. We're not aiming -- you know, 100 per cent is not haemostatically significant, necessarily. You might be aiming for 50 per cent or 40 per cent and that may be okay in terms of having a response to treatment, for example. You might consider a normal range to be down to around 50 per cent, like you said. It just sounds like it doesn't make sense.

I think there is a shift to move more towards units as an absolute term and I think it sort of depends on the laboratory standards that you are using as to which terminology you use to describe the resolve.

DR RYAN: Can I add something? Just to say that over many years now, all laboratories that test any of these biological values but particularly, you know, laboratories take part in national quality assurance schemes, so it means that a level in theory tested in one lab should be the same tested wherever that is. So it should

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be the same across the country.

SIR BRIAN LANGSTAFF: Thank you.

MS RICHARDS: Again, you may not be able to answer the next question, which is about numbers again, and it may be that we need to look at material from the National Haemophilia Database for that, but do you have a broad understanding of what the proportions are of those with haemophilia A in the country who would be classified as severe as opposed to those who would be classified as mild or moderate?

DR TUNSTALL: Broadly, if you look at the numbers under care, it does vary from centre to centre and may vary on diagnosis rates and referral rates, but moderate -- the severes, and non-severes tend to be of similar numbers with moderates as a lower number. But I think it depends very much on centre to centre.

DR GOODING: I'm afraid I've not got the absolute numbers, but the bleeding disorder statistics database is useful for that.

MS RICHARDS: Then I just wanted to ask a little about the bleeds themselves and potential significance of bleeds. You've described how someone with haemophilia A can bleed into the

closed spaces within the body, muscle joints, but also into the brain or gastrointestinal tract. Can you just tell us a little more about that. Tell us about the process by which blood is toxic to joint surfaces and tell us what "target joint" is, a phrase we've come across I think quite often in the evidence we've heard, and haemophilic arthropathy.

DR TUNSTALL: Fortunately, the bleeding into joints is a typical pattern in haemophilia. There appears to be something about process of, once there's blood in there, iron is a central component of blood, and iron is not reabsorbed very well and the process of bleeding, and particularly the iron, starts an inflammatory process in the joint in a relatively unpredictable way, but something that is associated with the more bleeding there is in a joint, the more likely that is to happen, although it can happen after one bleed or it may not happen clinically after ten or fifteen.

That can form a vicious cycle in that when you have more inflammation and more damage to the joint lining, that means that the joint is more likely to bleed. It often leads to

muscular imbalances around the joint and therefore you have a situation where once you've bled into a joint, you're more likely to bleed into that joint again and that causes progressive damage, and that damage can be very severe, and very disabling.

So the natural history of haemophilia, or particularly severe haemophilia without treatment, is progressive disability. With modern treatment, we hope to stop that process, but we -- but results of joints in people with haemophilia, even with modern care, are not perfect by any means and people with haemophilia end up having joint replacements at very young ages and other problems with their joints.

MS RICHARDS: You've explained in your report that without treatment these bleeds can be painful and debilitating and sometimes fatal. I just wanted to again explore that a little more because what you've also said in your report is that typically those with severe haemophilia may suffer severe disability and early death. I wondered what that suggestion might be based on in terms of any research or studies because presumably, for a number of decades, people with

severe haemophilia have been treated in a range of different ways. So what is the cohort of those who are without treatment that you're able to base those conclusions on?

DR GOODING: I suppose it's the historical perspective, really. So we know, you know, through the last sort of hundred years or so that life expectancy has improved with modern treatment. So if you're looking at just the absolute sort of life expectancy side of things, it's that sort of data, really. The modern study would be unethical in terms of treatments.

The more recent studies, I suppose, have been based on prophylaxis, so providing a level of Factor VIII ideally all the time to a certain degree, which have been shown in a number of studies over the years to improve overall joint health. That's true for starting, you know, this prophylaxis (so regular treatment) at a young age to protect joints has been shown to be beneficial in children against no treatment or on-demand treatment (so waiting for a bleed to happen). It's been shown in adults as well.

There's good high-level study evidence to support that and that's looking at joint health

and numbers of bleeds. I suppose there's sort of -- in some ways it's difficult to measure nowadays because the care has got better and better but it was looking at fairly crude measures like the number of bleeds that happened over a year sort of thinned.

DR TUNSTALL: The other comparative group is that haemophilia care remains very expensive and it's available in high-income countries but it's very uneven throughout the world and in many low-income countries, then children get very inadequate care for haemophilia, if any care at all.

MS RICHARDS: In terms of the kinds of bleeds that might, without any treatment at all -- and happily for the United Kingdom that is a historic position -- but without any treatment at all, what kind of bleeds could have been fatal? I can understand the kind of joint bleeds you're describing causing pain, potentially disability. In terms of bleeds that might be fatal, are we really talking about bleeds into the brain?

DR TUNSTALL: Bleeds into the brain, certainly; bleeds into the gastrointestinal tract, anywhere

down there; tongue bleeds could be fatal; bleeding from the gut, anywhere down the gut could be fatal; operative bleeding could be fatal.

SIR BRIAN LANGSTAFF: Presumably the effects of progressive immobility also has an effect in itself in shortening life.

DR TUNSTALL: One would imagine in general, yes.

DR SEKHAR: Can I just add, in some of the reports from the 1970s there are lists provided about the sites of bleeding and they're usually split into brain bleeding and other types of bleeding. The other types include this but also soft tissue; so bleeding into muscles is also a problem.

MS RICHARDS: Is there any data that you're aware of that would assist in understanding the frequency of those types of bleeds that you've just been describing (so the ones that can have a fatal outcome) in those with haemophilia A who receive treatment? It may be the answer is there isn't any.

DR TUNSTALL: I think it's very difficult to have good cross-sectional data without any treatment nowadays, to be able to understand numbers, yes.

MS RICHARDS: What we've been focusing upon there is something which would be predominantly a concern for those with severe haemophilia A rather than mild or moderate; is that fair?

DR GOODING: Mainly, yes. I mean, obviously it is possible that, like you said, postoperative bleeding can happen with mild or moderate haemophilia. Bleeding into the brain can happen as well and into the GI tract. So it's not entirely unique but it's a higher risk in --

DR TUNSTALL: It's rates of bleeding that really vary between severities and it would be unusual to see, as Richard describes, spontaneous bleeding in those with mild haemophilia, as it's termed. But bleeding still occurs and bleeding can be very significant, very serious.

MS RICHARDS: And do factor levels or the severity of a bleeding disorder fluctuate naturally over a person's lifetime?

DR TUNSTALL: In general, no.

DR GOODING: But for more mild disease you might see sort of fluctuations. So typically Factor VIII levels would be higher for the first six months of life and then bottom out and then maybe gradually rise. So it does depend a little bit on your baseline starting point. If there's no Factor VIII at all, it's not likely to change but if you have a degree of, you know, a sort of milder sort of level of reduction, then it can change.

We see that in female carriers as well. If a woman is a carrier of haemophilia and has a slightly lower Factor VIII level, which we do see, then typically those sorts of levels will fluctuate, a good example being in pregnancy where the levels may start at, I don't know, 25/30, something like that, and then normalise through the pregnancy and then drop back down again. So there is some variability, and I guess we'll touch on that later, but that tends to mirror the sorts of time periods where von Willebrand's levels can fluctuate as well.

MS RICHARDS: Before we talk about the different treatments that are currently available for haemophilia A, can I just ask you some questions about how one might manage the condition without treatment.

Now, I think both of you, your professional careers in relation to haemophilia have been in the recombinant era so these questions may not have much resonance for you, but advice about managing activity, advice about bed rest, advice about not undertaking certain activities, that can, in principle at least, form part of haemophilia care. Does it form much of a part of modern haemophilia care?

DR GOODING: Probably less so, but --

DR TUNSTALL: I mean, we -- so the philosophy in general, I mean certainly speaking about managing children with haemophilia these days is for them to lead as normal a life as is possible, and we try to facilitate them living a normal life. We do put certain limitations, and those limitations usually are don't take up rugby and don't do contact martial arts or boxing. But tends to be as limited as that.

There can be a case if there are certain activities that are particularly risky, then we would have discussions about them. So, you know, we have patients doing downhill mountain biking and just how you manage the risk associated with that, and we might have boys who are playing a high level of football who are seeing problems with their ankles, and you have to have realistic conversations. But it's

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generally a discussion about how best, how we balance risks and limit them as little as possible.

We do use rest, secondary rest in management after a bleed at times -- not usually bed rest as such, but a period of relative rest or non-weight bearing to help manage a bleed.

MS RICHARDS: Then before we look at any particular treatments, which we can do after the break, just talking about the philosophy of treatment, and again, these are questions about what you would currently do. The primary aim of treatment is to increase the levels of Factor VIII. That's why you would give treatment?

DR TUNSTALL: The primary aim of treatment is to allow people with haemophilia to have normal lives. To do that, we want to prevent bleeds. To do that, we want to increase the level of Factor VIII and/or if they have a bleed, then the primary way of managing that bleed is to increase the amount of Factor VIII.

DR GOODING: Just one other thing on that point, whilst that has been up until very recently the aim, there are some new treatments which

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technically don't affect Factor VIII but still have the same effect. So it is about reducing -- normal quality of life and reducing bleeding with whatever medicines we've currently got. But there are some newer treatments that have come out that are not quite doing that.

MS RICHARDS: You've alluded to this already but there are two broad concepts of a treatment programme: preventative prophylactic treatment which, as you've described in your report, might be long-term, particularly for someone who is classed as a severe haemophiliac, or might be short-term because surgery is planned; and then on-demand or reactive treatment which responds to there being a bleed. Is that broadly accurate?

DR TUNSTALL: Yes.

MS RICHARDS: Sir, I note the time.

SIR BRIAN LANGSTAFF: Yes, I just wonder if Professor Rockstroh would like to add anything to what has just been said over the last 20 minutes or so?

MS RICHARDS: Professor Rockstroh, before we rise, is there anything further you'd like to add at this stage?

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PROFESSOR ROCKSTROH: No, I think all the aspects were covered and it sort of reflects our own experiences well and so I'm all fine with what has been said and expressed.

MS RICHARDS: Thank you.

SIR BRIAN LANGSTAFF: I think we have to say goodbye to you at this stage, because your time is limited, Professor.

PROFESSOR ROCKSTROH: Yes, thank you very much.

SIR BRIAN LANGSTAFF: Thank you, thank you, enormously. It's been a privilege for us to have had you online, and in a busy schedule. So thank you very much indeed.

We'll take a break ourselves now for half an hour, to allow those who are listening to have coffee, or whatever. And we will return without you, I'm afraid, but thank you very much.

[Applause]

PROFESSOR ROCKSTROH: Thank you.

(11.33 am)

(A short break)

(12.04 pm)

MS RICHARDS: You set out in your report the current standard of care for a child diagnosed, first of all, with severe haemophilia. Can you tell us

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briefly what that is, what treatment you would typically expect a severe haemophiliac child to receive?

DR TUNSTALL: So we're actually in a little bit of flux at the moment, but I can -- the standard of care would be -- for a child with severe haemophilia would be to start preventative treatment with recombinant Factor VIII, at or before their first joint bleed. So typically we look at times when the child is going to become more mobile and more at risk of bleeding into a joint, so that can be around the age of one year. And in general, we try and prevent them having joint bleeds. As we talked before, that any joint bleeds can lead to damage, our feeling, certainly, as an institution, is the earlier we start the better. But there's an element of compromise. Often we need to insert a central venous catheter to give regular treatment, getting access to veins. Factor VIII can only be given into veins and getting access to veins in small babies is difficult. So the compromise measure is to start around a year, sometimes ten months, sometimes a bit after a year.

And we start regular what we call prophylaxis preventative treatment with recombinant Factor VIII, trying to maintain a baseline level of Factor VIII so they have protection from bleeding. And with that, we would aim that they don't suffer any bleeds at all. And certainly on any given year we would hope that most of our children wouldn't have any joint bleeds, certainly, or any significant bleeds. So they may require extra treatment for a bang on the head or something like that.

MS RICHARDS: Then again, typically, what would be the approach to a child who has either moderate or mild haemophilia?

DR TUNSTALL: So mild haemophilia is easy. We would not normally recommend what we call primary prophylaxis, that it would be unusual to require prophylaxis for anyone with mild haemophilia, and normally the approach is information and guidance and then treating problems as they come around. So if there is bleeding then we treat that, as we say, on an on-demand basis.

For moderate, then we are -- it's more controversial, let's say, or there's more things to consider. There's a certain amount of

evidence that in the last 20 years or so, as we've been better at starting primary prophylaxis in severe -- in patients with severe haemophilia, that actually the burden of disease has been pushed over to those with moderate haemophilia, so they have more problems with their joints than our children who started on early prophylaxis.

And so for that reason, for a child with levels of 1% or 2% as opposed to less than 1, we would be discussing giving primary prophylaxis. I think anything above 3, we would normally be taking a watch and wait process and only treating on demand, but we may consider if a child is having joint bleeds or having problems then we might do what we call secondary prophylaxis, where we start prophylaxis in response to a bleeding pattern rather than in anticipation of a bleeding pattern.

MS RICHARDS: Dr Gooding?

DR GOODING: Yes, it's just important to note that it's what -- the sort of rationale behind that is a risk assessment, obviously, between the numbers of bleeds, the severity of bleeds, and then the risks of treatment. So you can say,

why don't we just treat everybody who has a low Factor VIII up to normal -- you know, normal levels, and reduce bleeding risks altogether, but obviously the worry is the development of inhibitors, these inhibitory antibodies which render subsequent Factor VIII therapy very difficult or ineffective. And so that -- I think that that carries a bigger risk. So the severe -- obviously with -- with severe disease you've got a higher risk of permanent joint damage and more bleeding, and then as you move away from that, it's felt to be safer not to give regular prophylaxis and that's -- as Oliver has described, that's what we would do.

MS RICHARDS: You've alluded to inhibitors. Could you tell us briefly what inhibitors are, how they arise, and if you know what age they might typically emerge?

DR TUNSTALL: Inhibitors are basically antibodies against the infused Factor VIII. So the -- for many children particularly with severe haemophilia, they don't produce Factor VIII or don't produce normal Factor VIII, and the body's immune system doesn't recognise it as part of the body and will produce an immune reaction to

start producing antibodies against that. We know very well from international and national registers that that happens in somewhere between one and four and one in three children. They will start producing antibodies that stop the Factor VIII from working, and that's what we call an inhibitor.

The -- sometimes that's at a low level, and will quickly go away if we continue giving Factor VIII, and sometimes those antibodies are at a high level and can be very problematic for years, and sometimes indefinitely.

They typically occur within the first 20 exposures to Factor VIII, and typically occur fairly early on. So they typically occur in babies or young children. And they are a significant problem in haemophilia care.

We know that if we can't get rid of the Factor VIII inhibitor, then managing haemophilia is much more complicated as we can't give Factor VIII. We have to give something else which is going to help the body to clot.

MS RICHARDS: And do inhibitors typically emerge in childhood or can it be adulthood? Is there any particular pattern?

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DR TUNSTALL: So, with -- generally more common in severe haemophilia, we generally expose children with severe haemophilia to Factor VIII in early childhood because we're giving regular preventative treatment, and they generally occur in the first 20 exposures, so they almost -- in the context of severe haemophilia, they almost always occur in childhood. They can occur in non-severe haemophilia, and that risk is more spread out and can occur at other ages. And whilst the majority of inhibitors occur in childhood, they can occur at later age.

MS RICHARDS: What you have had described in the report is an initial management process that you term "tolerisation".

DR TUNSTALL: Yes.

MS RICHARDS: How does that work?

DR TUNSTALL: So, immune tolerance, we know from experience that if we can keep on exposing the immune system to the protein, to the Factor VIII, that often it stops producing an antibody response to it. And this is done by essentially continuing to give Factor VIII. And that can be done either what we would call low dose tolerance, which is at similar doses to

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standard prophylaxis given every couple of days, or it can be given in high dose daily, sometimes even twice a day, or of much higher doses of Factor VIII. And with that, about three-quarters, four out of five cases, we can get the inhibitor to go away to the extent that Factor VIII is an effective treatment once more.

MS RICHARDS: For those who don't successfully respond to that management process, treatment options traditionally have been, I think, FEIBA, and NovoSeven?

DR TUNSTALL: Yes.

So FEIBA is something we call activated prothrombin complex. FEIBA is its brand that it's sold under. It's a plasma-derived product which is -- basically contains a lot of activated clotting factors. Doesn't contain Factor VIII but it kind of bypasses and helps the blood to clot in the absence of Factor VIII.

Novoseven is a recombinant, so it's made in the lab, not taken from blood donations. It's an activated Factor VII. Both of them can be effective at treating bleeds, are effective -- not as effective as Factor VIII. People who have longstanding inhibitors have had far more

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problems as far as problematic joint bleeding, et cetera, than those who don't have inhibitors.

MS RICHARDS: Then there's a current treatment now, and I've been challenged to get the pronunciation of this right: emicizumab.

DR TUNSTALL: Pretty good. Emicizumab, or Hemlibra, has been a revolution in managing patients with chronic inhibitors over the last few years and is now coming into care for patients who don't have inhibitors. It's essentially -- it's an engineered antibody itself that -- it isn't Factor VIII but it does the job of Factor VIII.

And by -- it has the other great advantage that you can give it by a subcutaneous injection, so an injection under the skin rather than into a vein, so you don't need to have access to a vein, and you only have to give it once a week or once every two weeks. And it gives very effective protective treatment in patients with haemophilia, whether or not they have an inhibitor. So it works equally well in those who have anti-Factor VIII inhibitors.

MS RICHARDS: Then can I ask you to talk us through the current treatments for haemophilia A. Starting with recombinant Factor VIII, which is,

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I think, the mainstay of treatment now for haemophilia A. Can you just tell us what recombinant Factor VIII is? What it's made of?

DR TUNSTALL: Um --

MS RICHARDS: Or rather what it's not made of.

DR TUNSTALL: So recombinant factor VIII is made in a laboratory, essentially that it's made by cell lines, so these are cells taken -- mammalian cells not human cells, and they're treated so that they -- and genetically engineered so they -- the main thing they do is produce a lot of protein, and specifically Factor VIII. And -- so they produce Factor VIII to a certain -- at large volumes, and then that's isolated from -- extracted from that process and purified, and then put in vials and provided in concentrate and sent around.

MS RICHARDS: And the central idea behind recombinant Factor VIII, it's not made from human plasma?

DR TUNSTALL: It's not made from human plasma.

MS RICHARDS: You've said some products use human albumin in the extraction process. What is that?

DR TUNSTALL: Albumin is a major constituent of --

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it's a protein in the blood, in the blood plasma. For extraction purposes, I think a lot of the recombinant products would need to use some human proteins just to stabilise and extract the Factor VIII from the cell line. There are some newer products which don't use human albumin. Clearly, it's not being the -- the Factor VIII itself, it's not being extracted from plasma, and therefore we feel there should be a dramatically increased risk of viral transmission, we still think that the risk of viral transmission with recombinant Factor VIII should be vanishingly small, but because there are some human proteins involved in the manufacturing and some cases, then saying it's completely zero is beyond us.

MS RICHARDS: What considerations would you have regard to in deciding how much treatment is required to be effective for an individual? What do you look at about the individual in assessing the treatment you give?

DR TUNSTALL: Haemophilia care is quite standardised in the UK particularly. We have certain guidance. We plan treatment as a national body, through the UKHCDO, and -- and look at guidance

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which is written by the UKHCDO, and -- so within that there are certain parameters on starting treatment. So it -- it lays out -- in the UKHCDO prophylaxis guidance it lays out what would be a reasonable starting dose.

That dose would then be adjusted according to different parameters, basically, to the response to treatment, and the response to treatment would be based on bleeding levels, also baseline Factor VIII, measuring the levels and seeing if we're getting the expected target levels of Factor VIII.

We may adjust it, we are constantly looking at -- for example, in children, which is my area, that we'll be looking at their joints, looking at their activity, looking at any problems they may have, and looking for any signs that the treatment is inadequate or not working perfectly for them and adjusting on the basis of that.

SIR BRIAN LANGSTAFF: By "reasonable starting dose", presumably you don't give the same reasonable starting dose to a small young child as you would to a large, big adult?

DR TUNSTALL: On a per kilo basis.

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SIR BRIAN LANGSTAFF: So it's per kilo?

DR TUNSTALL: Yeah. It's still -- Factor VIII in general, there's a certain element of giving best bang for buck. That it's been expensive resource. So we're looking at effective dosing but it's not dosing to try and normalise factor levels, it's dosing to try to achieve factor levels that we know will prevent a certain amount of bleeding.

Whether that could still be improved, a lot of us argue we should still be giving more but we start at a basic dose per kilo.

DR GOODING: Just one extra thing with that, we do some monitoring tests as well, so -- as you've touched on already, but there are some -- there's some new software that can be used to -- to look at the response to treatment, so you can check a level sort of pre-dose and then after dose and then maybe a few hours later and then generate what we call a pharmacokinetic profile so you can actually graphically represent what the Factor VIII level is likely to be after a dose and when it might drop down to, say, 5 per cent, 3 per cent, 1 per cent, and maybe give a dose -- the next dose just ideally,

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I suppose, around the 3 to 1 per cent mark so it's both effective and efficient in a sense.

SIR BRIAN LANGSTAFF: Plainly the difference between somebody being given Factor VIII or making it themselves is that when they make it themselves, it's a constant process --

DR GOODING: (Nodded).

SIR BRIAN LANGSTAFF: -- and they constantly maintain whatever the level may be.

DR GOODING: Yes.

SIR BRIAN LANGSTAFF: If you give Factor VIII, is there a half life? Is that how it's put?

DR GOODING: Yes.

DR TUNSTALL: Yes.

SIR BRIAN LANGSTAFF: But what you're saying is that will differ from person to person?

DR GOODING: Yes, so typically it's much shorter in young children and it often gets to around about 12 hours or something like that, but it does depend on the product that's being given because -- we may come on this in a minute, but the -- there are some newer extended half-life products so there's ways of lengthening the half life, and then we would use that, that monitoring technique, just to see

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what happens. But there is a big variability between individuals, and so that's where that -- that sort of measuring step comes in.

DR TUNSTALL: I mean, just to say on that that if you're producing Factor VIII yourself, then, as you say, you get a constant level more and more, but -- but the curve is a decay curve so if we give a dose of Factor VIII you get a high point at the level that it's given and then it decreases quite rapidly down until it's really a very low level towards the end --

SIR BRIAN LANGSTAFF: You spoke --

DR TUNSTALL: -- (overspeaking) --

SIR BRIAN LANGSTAFF: -- about a baseline level earlier, is that the lowest to which you want it to drop?

DR TUNSTALL: The baseline level that we'd normally talk about is what -- is the baseline of endogenous Factor VIII, so that might be effectively zero for a -- for someone with severe haemophilia A. We talk about trough levels and trough levels are, again, an area where there are different beliefs, but we know fairly well that if you have a trough level that spends a prolonged period of time below 1

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per cent or below 3 per cent or, you know, the longer time you spend lower down there, then the higher the risk of bleeding. So we want to maintain good trough levels, and that's a fundamental part of the care.

MS RICHARDS: You've described in terms of frequency of treatment in your statement that when a child with severe haemophilia starts on this prophylaxis programme, it'll be three to four Factor VIII treatments a week, on average, subject to extended half life recombinant which will make it less frequent.

DR TUNSTALL: So normally every other day. Every 48 hours is our -- is our standard starting regimen.

MS RICHARDS: Is that something that continues at that frequency, potentially lifelong, or are you able to achieve longer periods between treatments?

DR TUNSTALL: In the absence of using extended half life products, then certainly in paediatric care we'd never recommend going beyond two days. Sometimes we end up giving daily treatment. If -- if the levels aren't good enough or the control isn't good enough with every other day

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dosing.

DR GOODING: That will be similar for the adult practice as well, really.

MS RICHARDS: And the extended half life recombinant Factor VIII may enable you to extend it to about every three days; is that right?

DR TUNSTALL: Yes, on average they -- they give about a 50 per cent extension of the half life, so on average if you gave a certain dose every two days of the standard molecule, you could probably give the same dose and achieve similar levels if you give it every three days, but that's on average and there's a lot of inter-individual variation.

MS RICHARDS: And then can we look just shortly at some of the other treatments that are still used for haemophilia A.

DDAVP, which we know has been around since the second half of the 1970s, that's a synthetic analogue of a naturally occurring hormone vasopressin; is that right?

DR TUNSTALL: That's right, yes.

MS RICHARDS: And that will increase the level of Factor VIII?

DR TUNSTALL: So that tends to increase the levels

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of Factor VIII if there is some Factor VIII to increase the levels of. Obviously for somebody not producing any Factor VIII, then Desmopressin and DDAVP is not likely to be effective. It causes release of the (inaudible) factor and Factor VIII from the endothelium, from the lining of the blood vessels, and you get an increase. It's very variable between individuals but, on average, maybe about four times the baseline levels.

So if somebody had levels of 20, then they might go up to 80. But then we'll reduce them down.

MS RICHARDS: So it's typically used for those with mild haemophilia or von Willebrand?

DR TUNSTALL: Yes.

MS RICHARDS: It's not used for those with severe haemophilia; is that right?

DR TUNSTALL: That's right.

MS RICHARDS: What about moderate haemophilia?

DR TUNSTALL: In general not in moderate haemophilia because normally if we're treating a bleed then we want to get levels higher than that.

MS RICHARDS: And you've said in your report it's not usually used for prolonged periods of time;

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why is that?
DR TUNSTALL: There's a blunting of the effect, so when you give the first dose, you get more release and a higher peak, and with subsequent doses you get a -- diminishing returns.

There's also concern about some of the side effects. So this is a physiologically active analogue, one of the things it does is cause fluid retention and disturbances of electrolytes, things like the sodium levels in the body, which can cause problems. And if you treat for a prolonged period of time you're more likely to run into problems too.
MS RICHARDS: But it's an effective treatment for those who don't require long-term prophylactic treatment?
DR TUNSTALL: It can be a very effective treatment, yes. It's situation-specific, and I think in the context of life threatening bleeding then we'd almost always be using a factor concentrate, but, but it depends on the situation. And it can be adequate for covering surgery, depending on the patient and the situation.
MS RICHARDS: Would you normally give a test dose

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before using it?
DR TUNSTALL: That's standard practice, yes.
MS RICHARDS: And why is that?
DR TUNSTALL: Just because of that variability in response. And -- and knowing what levels of response. There's variability in the -- the -- how long that's sustained for, both of which are important information to know before going into surgery, for example.
MS RICHARDS: Then plasma derived Factor VIII concentrates, you say in your report rarely used for haemophilia A in the UK. The figures that you've drawn from the National Haemophilia Database Annual Report show 13.4 million units of plasma-derived Factor VIII used for haemophilia A out of a total Factor VIII usage of 600 million units. So a small proportion but nonetheless not a vanishingly small one. When and why would plasma-derived Factor VIII concentrate still be used in modern practice?
DR TUNSTALL: To be honest, I don't know exactly where those 13 million -- I could talk about some of the places that we have used it. There is a certain amount of evidence -- we talked about inhibitors before, certainly

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internationally there is some thought that the rates of inhibitor formation are lower with plasma-derived Factor VIII. There's a certain amount of evidence but it's quite controversial, and in the UK we've generally taken the view that the downsides of plasma-derived Factor VIII for primary prophylaxis outweigh the possible upsides.

There's also evidence that in the context of immune tolerance for inhibitors, when we keep on giving the Factor VIII, sometimes it works beautifully, sometimes it doesn't work. And sometimes when it doesn't work we use extra measures, and one of those measures has been to try plasma-derived Factor VIII, and there's certainly cases where if we give recombinant Factor VIII immune tolerance and it doesn't work, if we change to a plasma-derived Factor VIII, it has worked, and it may well be -- and I don't know in the detail of those -- it may well be that there were people who have had inhibitors who have been tolerised with a plasma-derived Factor VIII. In that case we would stay on a plasma-derived Factor VIII.
DR GOODING: And it's worth noting that for immune

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tolerance reduction the amount of Factor VIII that you give is quite high, so that could explain -- I don't know, you know, for definite that these units -- but that could explain why there's a relatively high volume there.
MS RICHARDS: Then tranexamic acid.
DR GOODING: Shall I take this one?
DR TUNSTALL: Yes.
DR GOODING: So, tranexamic acid is a drug which essentially stable -- allows clots to remain stable without being broken down, so it's a useful therapy for generally mild sort of bleeding problems, particularly in the sort of mucosal kind of tract, so if you're looking at nosebleeds, gum bleeding, that sort of thing.

It's something we use if there's been that kind of bleeding in severe haemophilia and it's often used in mild haemophilia where, you know, if you're going to have a procedure of some sort, like a dental extraction, it could be very useful in that sort of setting. It's also used for heavy menstrual bleeding outside of the setting of bleeding disorders because it helps from that point of view as well. But it is used very widely.

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MS RICHARDS: I want to turn to ask you a little about haemophilia B now.

Now, haemophilia B is a deficiency of Factor IX. Again, could you just outline for us haemophilia B and how it might impact upon an individual and any material differences between haemophilia A and haemophilia B in that respect?

DR GOODING: Severe -- haemophilia B is actually very similar in a lot of ways to haemophilia A, in that the bleeding manifestations are very similar. The severity levels that have been taken are very similar as well. There's some argument as to whether it may be slightly milder for some people but essentially the Factor VIII and IX in the clotting cascade work, you know, at a very similar sort of level. So the -- you can see why -- why they produce this -- the same sort of disease, phenotype. In terms of differences, well, the inheritance is very similar. The half life of Factor IX is slightly longer, so that's a difference when we come on to, sort of, therapeutics. But otherwise, they are, sort of, very similar, really, in terms of management as well.

MS RICHARDS: And it's also classified, as

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I understand it, into severe, moderate and mild.

DR GOODING: (Nodded)

MS RICHARDS: Is it the same levels that are used for the classification as with factor (inaudible).

DR GOODING: Yes, yes.

MS RICHARDS: In terms of diagnosis, again, a similar --

DR TUNSTALL: Very similar process, yes.

DR GOODING: So the same blood test would be effectively -- you know, we talked about the prolongation of the APTT clotting time, so it's the same -- you see the same picture if you're doing a coagulation screen, you get this isolated -- the isolated prolongation of the APTT, and then, in the same sort of way, if you're suspecting a bleed, you'd go on and check that. So I suppose if you're looking at a newly diagnosed child, for example, with bleeding manifestations, the coagulation screen would be done, the APTT would found to be prolonged, and then typically what would happen from there is that you'd -- you'd actually do all the clotting factors that are affected. So within APTT we would check Factor VIII, Factor IX, Factor XI,

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and Factor XII, which less relevant. And so that -- in that respect, we would pick up haemophilia A, haemophilia B, and then take it from there.

MS RICHARDS: Again, it's something that can occur within families or, as with haemophilia A, occur spontaneously?

DR GOODING: Yes.

DR TUNSTALL: Yes. Basically the way it's inherited it's a gene on factor -- on the X chromosome, and it's got the same patterns of inheritance.

MS RICHARDS: Is there any material difference between haemophilia A and haemophilia B in terms of the risks without treatment and the way in which bleeds occur?

DR TUNSTALL: Not clear differences, no. No. There's differences in treatment and response to treatment. There's difference in inhibitor rates and the patterns of inhibitors with haemophilia B, but as far as without treatment, then there are no significant differences.

MS RICHARDS: And in terms of treatment in the case of those who develop inhibitors, FEIBA can be contraindicated; is that right?

DR TUNSTALL: It's a relative contraindication. The

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problem with inhibitors in haemophilia B is they often take an allergic form and sometimes they can give rise to a very severe allergic reaction, what we call an anaphylaxis. The problem with FEIBA is it contains Factor IX. So for those who have got an inhibitor, it is still sometimes used in patients with inhibitors against Factor IX but it can cause problems.

MS RICHARDS: But current treatments for haemophilia B, the primary treatment is recombinant Factor IX; is that right?

DR TUNSTALL: Yes, so Desprovassin doesn't work, and we use tranexamic acid in a similar way. There is some use of plasma-derived Factor IX. The recombinant Factor IX is also used, plasma-derived Factor IX is probably in -- I don't have the statistics to hand, but I'd imagine --

MS RICHARDS: 4.5 million units out of a total usage of 80 million according to the last National Haemophilia Database report.

DR TUNSTALL: Yes, so a bit higher. There are those who seem to respond better to plasma-derived Factor IX or to have better pharmacokinetics with plasma-derived Factor IX than with

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recombinant Factor IX.
MS RICHARDS: In terms of the recombinant Factor IX, the frequency of injections can be less than the frequency of injections with the Factor VIII?
DR TUNSTALL: That's right. It naturally has a longer half-life, which means that in general a standard dosing might be twice a week with a standard molecule but it's also true the extended half-life molecules are more extended for the Factor IX than they are for Factor VIII. In those cases weekly dosing is typical.
MS RICHARDS: You've said you can even achieve fortnightly dosing in some cases?
DR TUNSTALL: Yes.
MS RICHARDS: Then haemophilia C, or Factor XI deficiency. Could one of you just outline that for us, please.
DR GOODING: So it's a sort of -- it is -- this is a very different sort of situation, really. So this is Factor XI deficiency. It's typically characterised by more of a very variable disorder, and so we don't see this sort of correlation between factor levels and bleeding phenotype, this sort of type of disorder you get. So it's not like we can say, you know,

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these levels are less than 10 per cent or less than 1 per cent. We're going to see joint bleeding or bleeding problems, so we don't -- that's a really important difference with this disorder and how it presents and then obviously how it's treated.
We typically see a different sort of bleeding pattern as well. Classically, it's areas where there's a sort of what we call high fibronetic activity. But typically we see, I suppose, bleeding into the mouth or mucosal-type bleeding. It can complicate surgery as well. But it's not something that tends to present with sort of spontaneous bleeding into joints and muscles.
MS RICHARDS: You've said it's often asymptomatic and most commonly problematic after surgery or trauma, sometimes?
DR GOODING: Yes, that's fair to say, and we may see it manifesting itself with heavy menstrual bleeding or postoperative sort of bleeding.
MS RICHARDS: There's no recombinant Factor XI or treatment for this condition?
DR GOODING: Yes.
MS RICHARDS: Is that right?

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DR GOODING: That's right.
MS RICHARDS: It's plasma-derived Factor XI concentrate which is the mainstay of treatment when it is required?
DR GOODING: Yes and very much when it is required. So it is quite unusual to require a Factor XI replacement in this sort of disorder. Most of the time the bleeding phenotype is mild and usually we would use adjunctive sort of measures like tranexamic acid. The slight concern with some of the concentrates there's been an increased risk in thrombosis. So when it is given, it's given in a very carefully considered way and usually at a lowish dose.
MS RICHARDS: We can see from your report an idea of the kind of figures of those who might receive the Factor XI concentrate which is produced, as I say, from human plasma. Forty-five patients received Factor XI in the UK in 2018/19 which is 1.3 per cent of registered patients with deficiency.
As well as tranexamic acid which you've described as remarkably effective for Factor XI, fresh frozen plasma is also used?
DR GOODING: That's right, yes, quite often I think

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because of those concerns about thrombosis.
MS RICHARDS: Then von Willebrand disease, can you tell us what that is please.
DR TUNSTALL: Shall I take that?
DR GOODING: Yes.
DR TUNSTALL: Von Willebrand disease is a disorder of the von Willebrand factor protein which is a -- so it can either be low levels or low functioning levels of von Willebrand factor. Von Willebrand factor is quite central to coagulation in two parts. It's involved in platelet aggregation and adhesion, which is very important for clotting, and it's important because it stabilises Factor VIII in the circulation.
It's classified in different ways: so a type 1 where you have reduced levels of von Willebrand factor and reduced function with those levels; type 2, where often as well as the low levels, it doesn't function normally so there's a mismatch between its activity and the amount of the protein in the blood; and type 3, where you have effectively undetectable levels.
Type 2 is further classified. There's type 2A and type 2N, where -- which are -- you

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basically have von Willebrand factor at low levels but it doesn't work so well. 2N is a particular type where it doesn't bind Factor VIII so you get low levels of Factor VIII. 2B is to do with this interaction with platelets and it binds overly eagerly to the platelets.

MS RICHARDS: What you've said is in the report is that there can be diagnostic uncertainty in von Willebrand. You'll have people with a clear tendency to bleed and bruise, but that wouldn't necessarily be reflected in the VWF levels, and then some people may have a tendency to bleed with low levels, some may have low levels but not a tendency to bleed. Is that right?

DR TUNSTALL: So there can be a very clear diagnosis of von Willebrand disease where you have very clearly reduced levels and a bleeding type. Then there is a group where the levels are somewhat lower than what we consider the normal range, and often in those cases it's been called von Willebrand's disease.

There's a certain question in some studies whether -- the problem is that if somebody presents with bleeding problems and nosebleeds,

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then we do a lot of tests. If one of those tests comes back abnormal, then it's the belief that that is causing the bleeding problems. Perhaps it's not always the case. I think in von Willebrand disease that's sometimes the case, so it's not 100 per cent clear in those cases with lowish levels, but not very low levels, that the low von Willebrand factor is causing the problem and there's a bit of caution about the diagnosis for that reason.

DR GOODING: Typically it is a milder sort of disorder with a very variable picture and the pattern of bleeding again, as opposed to, say, the haemophilia A and B we've talked about it, tends to be the sort of mucosal type, the sort of primary haemostasis which is affected, so you get easy bruising, nose bleeding, gum bleeding, that sort of picture rather than a deep tissue bleeding, except in perhaps type 3 where Factor VIII levels are low as well.

MS RICHARDS: So it's in that category you might have what you describe in the report as haemophilia type bleeding?

DR GOODING: Yes.

MS RICHARDS: Again, is this something that would

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predominantly run in the family but it also occurs spontaneously or is it roughly equal proportions?

DR TUNSTALL: I don't know the proportions.

DR GOODING: I'm not sure either, actually.

DR TUNSTALL: If anything, it -- there seems to be more cases with familial links on the rise.

DR GOODING: Much like with haemophilia, there is an acquired form as well, but that's very rare.

MS RICHARDS: Are there any -- or what are the diagnostic criteria, given that there may be a slightly more complicated presentation in relation to von Willebrand, are there guidelines, standards, criteria, thresholds by which you would diagnose von Willebrand? Are there risks of misdiagnosis or conditions that need to be excluded?

DR GOODING: I suppose the diagnosis is -- well, it depends a little about why you suspect it in the first place, I suppose. If you've got a family history then you can cautiously pursue testing in the early sort of phase of life but it is worth noting that the levels will not normalise until 6 to 12 months of age. So, yes, you can do the same sort of testing we talked about for

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screening for haemophilia A with cord bloods and that sort of thing but, actually, you may miss diagnosis in that sort of setting so you do need to be cautious if you're doing tests in the early phase of life, you know, if you're screening for a known disorder in the family. So that's really important just to -- that the levels do fluctuate, that we talked about earlier on.

The other time I suppose you'd be testing for it would be if you had an abnormal child with easy bruising, for example. It's quite often picked up in the setting of screening for non-accidental injury, for example, or maybe later in life if there's postoperative bleeding or heavy menstrual bleeding, those sorts of things and that's where bleeding symptoms are felt to be out of keeping with normal, then that will be a time to do further haemophilia static investigations.

DR TUNSTALL: There is a national guideline from UKHCDO which we try and follow, which details some of the details of the testing. It is -- it's more complicated, the different aspects of testing, than simply doing a Factor VIII level

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in haemophilia A.
MS RICHARDS: Then inhibitors can occur with type 3 but not type 1 or 2?
DR TUNSTALL: Yeah, I don't know that they're reported in type 1 or type 2. So yes, they do occur at times in type 3.
MS RICHARDS: What's the primary treatment and the approach to treatment for von Willebrand's?
DR TUNSTALL: Generally it's reactive rather than preventative. Depending on the patterns of bleeding. Even in type 3 von Willebrand's disease, the patterns of bleeding are very variable, and some people don't bleed to -- from year to year, and so it tends to be managing issues as they come up. Those issues may be around recurrent nosebleeds, about bleeding from the mouth. They may be around heavy menstrual bleeding and managing that.

There's a number of issues, they may be more trauma-related, so in response to injury or covering surgery or dental procedures, so it's depending on the situation.
MS RICHARDS: If treatment is required, is it most likely to be DDAVP or tranexamic acid or something else?

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DR TUNSTALL: Well, depending on the levels. So again, it depends on the baseline levels, and the baseline activity of the von Willebrand factor, and it depends on the situation as to whether DDAVP or tranexamic acid, or factor concentrate, so factor concentrate would be often talked about plasma-derived Factor VIII also contained von Willebrand factor. They vary slightly in how much von Willebrand factor they contain but there are products that are particularly designed and marketed as for treatment of von Willebrand factor, and they're used.
MS RICHARDS: So there's no recombinant equivalent for VW?
DR TUNSTALL: There is a recombinant von Willebrand factor that's just come to the market now. It is not licensed for prevention or licensed in children and I don't think it's yet funded in the NHS, but it's recently been developed and so we don't quite know how that's going to fit in, and where it will be most used.
DR GOODING: Just one thing about treatment as well is that in the paediatric cohort, if a child with more severe von Willebrand disease needs

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treatment we don't use DDAVP in that sort of setting. So typically after the age of maybe two or three years it's felt safe but before that, because of the changes with fluid retention, there's a risk, particularly, of sodium levels dropping and causing fits and seizures, so we don't tend to use it in that -- so if there is a need for treatment in that group, they tend to have the plasma-derived von Willebrand concentrate, then after that we would do the DDAVP tests and use that more often.
MS RICHARDS: You've drawn attention in your report to particular problems that women, and I should make clear, women will suffer from von Willebrand's, *(Witness nodded)* is it equally as much as men or is it more women than men?
DR GOODING: The same.
DR TUNSTALL: One would predict equal numbers but possibly reflecting that there are particular difficulties for women with von Willebrand disease. There are more women registered in the UK with von Willebrand disease than men.
MS RICHARDS: And the particular problems they can experience can be related to menstrual bleeding?

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DR TUNSTALL: Menstrual bleeding can be a big problem in von Willebrand's disease, yeah.
MS RICHARDS: And pregnancy. There can be a severe drop-off in VWF levels after delivery and a risk of post-partum haemorrhage.
DR TUNSTALL: Yes.
DR GOODING: Yes.
MS RICHARDS: There's a handful of more general questions I have about bleeding disorders, rather than specific to the four that we've looked at.

Life expectancy, so I'm not asking you to comment upon life expectancy for those with hepatitis C or HIV, we've heard some evidence from others in relation to that but just generally in terms of life expectancy nowadays for somebody with any of the forms of haemophilia or von Willebrand that we've discussed. What's known about that?
DR GOODING: I think typically we would expect life expectancy to be approaching normal now. The -- I suppose having inhibitors may affect life expectancy but, essentially, my feeling is that we're seeing patients with or people with haemophilia, rather, growing into an older age,

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and that's evidenced by the fact that we're starting to see some of the diseases of older age as well, and that's an area of particular interest to some clinicians now.

MS RICHARDS: Does having a bleeding disorder impact upon a person's susceptibility to infection more generally, as far as you know?

DR TUNSTALL: I don't think we've found clear evidence to that, no. I mean there is theoretical considerations that the clotting system and the immune system are not entirely disconnected but I don't know of any clear evidence to suggest that.

DR SEKHAR: If may add.

MS RICHARDS: Yes, absolutely.

DR SEKHAR: Because bleeding, when you say bleeding disorder, we've been talking so far about inherited conditions but when people have severe bleeding and they are given blood transfusions, there is some suggestion that blood transfusions, especially red blood cell transfusions, can affect a person's immune system and it's easier to acquire infections. It's relatively new areas in the literature.

MS RICHARDS: Thank you. Can I just explore in

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relation to haemophilia, some issues relating specifically to women. What's the difference between someone with haemophilia and a symptomatic carrier? Is there in truth a difference?

DR TUNSTALL: Not in my opinion. A symptomatic carrier has often been used, I don't know why we use that terminology particularly, but there are women who have low Factor VIII levels, therefore they have haemophilia in my view.

DR GOODING: That would be my opinion as well, actually.

MS RICHARDS: Thank you. Then I've just -- some questions about aspects of modern haemophilia care. Am I right in thinking it's still organised through Haemophilia Centres?

DR GOODING: Yes.

MS RICHARDS: And it's a form of specialised care, and you've referred already to some of the standards that are set for haemophilia care through UKHCDO. I wanted to look at a couple of aspects of a set of quality standards.

Henry, could we have EXPG0000029, please. These are described as:

"Quality standards, care of people with

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inherited and acquired haemophilia and other bleeding disorders, July 2018."

I think we've discussed this before you've come in, you're broadly familiar with this document. There were two aspects of it that I wanted to ask you about so if we could go, please, Henry to page 12.

DR TUNSTALL: Is it worth contextualising what these standards are?

MS RICHARDS: Yes, please. Yes.

DR TUNSTALL: One of the processes of ensuring good care for people with haemophilia is a process of what we call peer review, whereby each centre, so Haemophilia Centres are organised into what we call comprehensive care centre, which would be a specialist regional centre, and then haemophilia care -- haemophilia centres who will manage the day-to-day care of patients who are closer to that town, but usually will be linked in with a comprehensive care centre, and there is a peer review process where clinicians from different centres go and assess the care of people with inherited bleeding disorders in different centres, against different criteria, and these are the criteria that are used.

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MS RICHARDS: Are these standards that every comprehensive care centre is expected to meet in every respect or are they more aspirational?

DR TUNSTALL: Without pre-judging the results of the recent round of peer review I don't imagine any centre reached every standard, and some of them are probably more aspirational than ...

MS RICHARDS: I'm going to ask you about two aspects of them, so if we go to the bottom of page 12, please, Henry. Thanks.

We've got a heading:

"Staffing levels and skill mix."

If you look down towards the very bottom of the page we have (e):

"Clinical or counselling specialist psychologist or appropriately trained psychotherapist."

So this sets out -- I use the words relatively an aspiration or a standard that staffing should include, amongst the other specialities that are set out there, a specialist psychologist or psychotherapist.

Two questions arising from that, first of all, do you have any sense as to the extent to which that's achieved in practice in Haemophilia

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Centres?
DR TUNSTALL: Yeah, I suppose on the use of term "aspirational", I'm just going to slightly roll back. I think it is laying down what we think should happen. That doesn't mean that every centre is able to do that and whether the funding is in place for every centre to do that is right.
DR GOODING: It's useful to have a framework like this set out by the UKHCDO so we can then say to our hospital, I can say to my boss, "Actually, I need this", and then we can try and work towards having the things that we may not currently have to provide this standard. I suppose, yeah, but ...
DR TUNSTALL: So we have a psychologist very much embedded within the multi-disciplinary team treating -- looking after families with children with haemophilia and it's a vital part of the service, we think. I don't think -- I'm fairly sure not every centre has the same access to psychologists.
MS RICHARDS: Would you expect the focus of the psychology expertise that might be delivered in those centres which do have a psychologist to be

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counselling and support in relation to haemophilia and other bleeding disorders, or would you expect them to be able to provide specialist psychological support in relation to hepatitis or HIV?
DR TUNSTALL: In general, speaking for our service, that they will try and support any aspects of care. But sometimes, when there's interaction with other services, then it may be that there is more specialist provision within those other services. So we wouldn't necessarily expect that our clinical psychologist would be an expert per se in issues relating to hepatitis or HIV, but would be an expert in dealing with psychological trauma and having expertise in different modalities which may well be applicable, or be able to tie in with signposting where there may be other support.
But I think in general, my experience is that support from psychology services is very patchy, within the NHS in general.
DR GOODING: Yes, I would agree with that. We have access to psychology services but we don't have a specialist psychologist and I wouldn't expect them to have a great deal of experience with

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individual disease conditions or certainly not a combination, necessarily, of disease conditions.
MS RICHARDS: Then before we break, sir, just one further question in relation to this document. If we go, please, Henry, to page 16, we can see at the top of the page under the heading "Specialist services" it refers to:
"Timely access to the following specialist staff and services should be available as part of an HCC service. HC should be able to access these services through network arrangements and we see a range of different types of specialist service including at J HIV services and H hepatology."
As I understand this document, please correct me if I'm wrong, what this is envisaging is that where you have a patient under the care of your centre, who may have needs that fall within any of these areas, you would expect to be able, as it were, to make a referral or put them in touch with the relevant specialists. You wouldn't be offering those specialist services yourself?
DR TUNSTALL: That's correct. More than that, we

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would expect some kind of relationship and communication with those services, to facilitate the particular care that our patient group would need.
SIR BRIAN LANGSTAFF: I'm sorry, I interrupted. I beg your pardon.
What this would mean would be, would it, that someone who was a haemophiliac who had HIV infection or hepatitis infection or both, could get the services of a psychologist who knew about haematology but not necessarily about HIV or hepatitis or could be referred to someone who is a psychologist working within the HIV and hepatology services -- hepatitis services who knew nothing very much about haematology?
DR TUNSTALL: Talking about -- going back to the previous issue, I think it's possible they may have access to a psychologist with expertise in haematology but not HIV or hepatology. They may have access to a psychologist with expertise in hepatitis and HIV care. They may have access to both or they may have access to neither, and that's where I mean it's extremely patchy and I don't think -- different centres organise services in different ways, and many services

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don't really have access at all or only have access to a general provision which is often after a very long wait.

MS RICHARDS: This particular standard is not, in fact, concerned with psychology as such but concerned with those who might need care for their HIV or their liver. You would not be providing that or treatment in relation to that within the modern Haemophilia Centre, but you may make specialist referrals and we see later on in this document there is a reference to the possibility of having multi-disciplinary clinics.

DR GOODING: Yes.

DR TUNSTALL: I think that's correct. There would either be an expectation of established pathways for referrals, for patients to access those services, or a joint clinic.

MS RICHARDS: But you'd expect in the modern era treatment and care for HIV or hepatitis to be undertaken by specialists in those particular fields.

DR GOODING: Yes.

DR TUNSTALL: I would, yes.

DR GOODING: I think it's worth noting here as well

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with specialist services, unlike perhaps psychology services, it would be unthinkable that a Haemophilia Centre wouldn't have access to HIV services and hepatology. That would be, you know, an absolute expectation.

MS RICHARDS: Sir, is that a convenient point to stop?

SIR BRIAN LANGSTAFF: Yes, it is. Two o'clock. We'll take break. Two o'clock.

(1.04 pm)

(The luncheon adjournment)

(2.05 pm)

MS RICHARDS: I'm going to move on to ask the panel to consider transfusion-dependent disorders, and in particular the inherited disorders of haemoglobin. Could I start by asking you perhaps to tell us what haemoglobin is and what these disorders -- what problems these disorders generally cause?

DR RYAN: Okay, so haemoglobin is the substance in our red blood cells that carries oxygen around the body, and we -- so the haemoglobin -- so we need to -- to obviously provide oxygen. And we have a number of disorders that are very common across the world that affect the amount of -- or

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the amount or the structure of the haemoglobin that circulates in the red blood cells, and these disorders are genetically inherited, and probably have arisen over the years because they did confer a certain sort of resistance to malaria and that's why they're very common in parts of the world where malaria was or is very prevalent.

So haemoglobin is carried in the -- it's got an iron-containing molecule and has these protein chains, and the thalassaemias are disorders that affect the production of the protein chains, whereas sickle cell disorders affect the actual type of haemoglobin. So they are different disorders and they have different clinical consequences.

So I'll start with thalassaemia. So the thalassaemias affect, as I say, the protein component of haemoglobin. They are very prevalent. They are the commonest genetic disorders across the world. They're divided into the alpha thalassaemias and the beta thalassaemias, depending on which of the protein chains is involved, and the end result is you don't make enough haemoglobin and this results

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in anaemia and it results in very small red blood cells.

Because of the -- there's hundreds of different types of mutation affecting the beta thalassaemias and therefore a very different range of clinical spectrum of anaemia and disorders. So the alpha thalassaemias are usually not too much of a problem clinically although in some parts of the world, for instance in south Asia, China, there is a sort of moderately severe form of alpha thalassaemia that can require transfusions, but the commonest type of thalassaemia we encounter here in the UK as serious thalassaemia are the beta thalassaemias.

We can divide those thalassaemias into those that are severe enough to need blood transfusion and those that don't need blood transfusion. But, as I say, the genetic basis of this is very complicated and really a lot of it depends on the part of the world that you came from, although we see quite a big spread across the UK now.

So the problems of thalassaemia are related to anaemia. If you don't have enough blood

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cells, you're going to feel very tired. If you're a child and you don't make enough haemoglobin, you're not going to grow and develop, and your bone marrow tries to compensate by expanding, this causes expansion of the bones and causes bone problems and sort of a -- sort of skeletal enlargement, and expands by -- the liver and the spleen expand as well.

And generally if you're a child born with severe thalassaemia, you don't grow and survive, and without any kind of blood transfusion treatment you would typically die in the first decade of life.

The other problems that we see are related to the iron overload. So we can treat thalassaemia with regular blood transfusions but each blood transfusion carries with it a certain amount of iron, and the iron cannot be -- our bodies cannot get rid of iron very easily. So the iron is retained by tissues, and the iron particularly is retained in the liver, and it is retained in the heart, it also affects the endocrine glands, and -- it really affects a number of other organs in the body.

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So iron causes inflammation in excess, and this leads to chronic liver disease, namely liver cirrhosis, and increases the risk of liver cancer. In the heart, excess iron can cause heart failure and heart rhythm disturbances, and excess iron in the endocrine glands causes problems such as diabetes, low thyroid, failure to grow and develop, et cetera.

So the problems are really both due to anaemia and iron overload, and there is a sort of mix of both of those which -- it varies from individual to individual depending on the type of thalassaemia they have, and the type of treatment that they have as well.

So it's a chronic disorder. People who are transfusion-dependent will normally need blood transfusions every -- between every two and six weeks. And they will need to take treatment really from the first year or so of life with iron collation treatment. These are drugs that actually remove the iron from the blood.

And they will need to attend -- so, as I say, for blood transfusions, and regular clinic appointments and all sorts of specialist investigations to monitor for the affects of

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iron overload.

So that's sort of thalassaemia in a nutshell. Do you want me to proceed with sickle?

MS RICHARDS: No, we'll come on to sickle cell in a few minutes. Just a few further matters arising in relation to thalassaemia.

There's a national haemoglobinopathy registry.

DR RYAN: Yes.

MS RICHARDS: And you've recorded in the report that as of September 2019 the numbers on that registry were 1,921 with thalassaemia and, just to complete the figures, for sickle cell, which we'll discuss in a few minutes, 13,675. And then some rare anaemias which we'll also come on to later, 460, although that may be, as I understand it, something of an underestimate.

Just in relation to thalassaemia, you've also said that those who will require regular blood transfusions is in the region of, I think, 900 to 1,000. And that's a lifelong requirement, is it?

DR RYAN: Yes, yes. But many patients who don't require regular transfusions from childhood may

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start to need transfusions in adult life for a variety of reasons. I think over the years we have intended to lower our threshold for transfusion because we have better drugs to remove iron, and we realise that chronic anaemia is really quite disabling for thalassaemia patients.

MS RICHARDS: And we know from evidence that we've heard that people with thalassaemia who received regular transfusions developed hepatitis C. Is there any data of which you're aware which tells us how many were affected in that way?

DR RYAN: No, I think is the answer. I did -- I did try and make enquiries to see whether we had that information, but I don't think we do. But the problem is that a lot of -- we have a lot of patients arriving in the UK from abroad who acquired hepatitis abroad and we don't, therefore, know how long they've had it, how they acquired it, and we don't know -- we haven't really got reliable data on -- on deaths from -- deaths from sort of iron overload as opposed to other causes of liver disease. So -- so we don't really -- in a nutshell, we don't have that information although we are sort of

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starting to collect it now.
MS RICHARDS: And you described symptoms associated with either thalassaemia or the iron overload, consequences of thalassaemia, fatigue and so on, which obviously may be very similar to the symptoms that an individual might experience with hepatitis C. Do you know whether there were problems of delays in people being diagnosed with hepatitis C because they didn't know that their symptoms were attributable or might be attributable to something other than their iron overload?
DR RYAN: I don't know for a fact. I would imagine that that is the case. Hepatitis C screening of blood only came in in the early 1990s. We knew patients had chronic hepatitis but we didn't know to what extent the iron in the liver was contributing. So it wasn't very clear because there's a number of mechanisms of liver disease in thalassaemia.
MS RICHARDS: And the risk of a person with thalassaemia and chronic viral hepatitis developing liver cancer is, as I understand it, compounded by the problems of iron overload?
DR RYAN: Absolutely, yes. Yes.

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MS RICHARDS: Which can result in fibrosis, cirrhosis and cancer?
DR RYAN: Mm-hm.
MS RICHARDS: Is there any data about the impact on life expectancy for a hepatitis C positive individual with thalassaemia against someone who has thalassaemia but no hepatitis?
DR RYAN: I don't know of any UK data. I think there will be data from other parts of Europe where hepatitis C is much more prevalent.
The life expectancy of thalassaemia is changing all the time because we now have much better ways of treating iron overload and we are much more able to assess more accurately how much iron is in the body through imaging scanning, so we're much better at treating iron overload. So we think our life expectancy for our thalassaemia patients is -- you know, providing they take the treatment, should be approaching, you know, near normal now. There are other treatments coming on board for thalassaemia as well.
MS RICHARDS: That are not transfusion dependent?
DR RYAN: Yeah. So there are -- we're on -- we have new drugs in development that will improve the

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haemoglobin, and we have a gene therapy, it's -- and a new exciting prospect for thalassaemia which is under consideration at the moment.
MS RICHARDS: Then are there particular difficulties for someone with thalassaemia who has hepatitis C, or indeed HIV, that are compounded -- other than the liver consequences we've discussed, that are compounded?
DR RYAN: Well, I've never seen a thalassaemia patient with HIV. Whenever we get a patient with hepatitis C, and we do still see patients as they arrive from other parts of the world, they are managed with the liver teams, as in the other disorders. The treatment itself can compound the fatigue that they get and also some of the older treatments used to increase the amount of haemoglobin so they would end up needing more blood transfusion.
MS RICHARDS: Can I ask you to turn to sickle cell disorders and tell us a little bit more about those?
DR SEKHAR: Can I just comment?
A really important part of thalassaemia is, as Kate was saying, to get rid of the iron, and until a few years ago it was mainly injections,

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subcutaneous injections, which had to be injected at night, or during the day, but kept going, as a syringe, for the best part of 8 hours or so. For young people, it was very difficult. So compliance was very difficult, and going to college or uni or senior school was very difficult. So many of them have now been able to move on to oral chelation but even that is fraught with a lot of --
DR RYAN: Adherence is still a big issue. The drugs themselves are mostly non-toxic but they need monitoring, but I think with any chronic disease, adherence is -- is an issue, for patients.
MS RICHARDS: And the point you've just made adds to the treatment burden for the patient.
DR RYAN: Yes.
MS RICHARDS: We discussed that in other contexts but if you are a patient with thalassaemia who is having also to be treated for the consequences of iron overload and having to receive what we know were horrific treatments in terms of side effects for hepatitis C, prior to the modern era of treatment, that can be a significant physical and psychological burden

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for the individual.
DR SEKHAR: Plus the monthly blood transfusions.
MS RICHARDS: Of course.
DR RYAN: I mean, there is -- there has been some recent study which is looking at the real life experience in -- and it shows that the quality of life is -- is about 65 per cent. If you look at quality of life indicators, it's about 65% for thalassaemia patients compared to a normal population, and that's even with safe blood transfusion, reasonably, you know, effective chelation. So it's still -- it is a considerable psychological burden.
MS RICHARDS: And that's before you add the burden of hepatitis C treatment?
DR RYAN: Yes.
MS RICHARDS: Sickle cell disorders.
DR RYAN: Sickle cell disorders refer to a group of conditions where the basic problem is a mutation in the haemoglobin molecule to produce a substance called haemoglobin S. And haemoglobin S, under certain conditions of low oxygen or other conditions, causes the red cell -- precipitates, if you like, in the red cell and deforms the red cell into

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a characteristic sickle shape. And these deformed red cells are not very pliable, they don't pass through vessels very easily, so they block vessels, and they cause inflammation and they cause all sorts of problems.

Now, it's -- the sickle disorders really -- we refer to sickle cell disease, which is a number of different types of sickle cell. The most common in the UK is what we call SS, which is about two-thirds of patients, and the rest are SC -- SC, a mixture of other genetic problems.

Sickle cell gene has arisen in Africa, so most of our patients with sickle cell are of African origin, either black African, black British, black Caribbean, and that's about two-thirds of the patients. The sickle cell gene is also, however, found in the Middle East, parts of southern Europe, and in parts of India as well. So it's a sort of -- a disease that affects predominantly non-Caucasians, but increasingly it's seen in all different ethnic groups.

So the problems of sickle cell, it's a multi-system disease, and any part of the body

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can be affected. You can divide the problems into acute problems or chronic problems. So the acute problems, I think the single most difficult problem for patients is episodes of pain, called the painful crisis. These are -- can occur very frequently in some patients, and cause excruciating pain in different parts of the body. And often the pain is -- it will require strong painkillers, including morphine. Patients need to be hospitalised for pain management.

That is very variable. The number of crises a patient gets is very variable, it can be none a year, but most people will get episodes of pain of varying severity, and some patients can be in hospital 20 times a year for a painful crisis.

Patients with sickle cell are anaemic. They run a haemoglobin a lot lower than a normal haemoglobin, and this can be made worse during a crisis or during an infection. They're very prone to infections as well because the spleen, which is important for processing bugs, doesn't work in sickle cell. So infection, particularly with certain bacteria, is a big problem. And

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malaria is a big problem as well.

And another major problem for children is stroke. So about 10% of sickle children will get an overt stroke, with about another 20% of sickle children getting, sort of, brain infarcts, which may not be manifest as sort of an obvious physical disability but will affect all sorts of cognition and learning and et cetera.

So all these different -- there are a lot of different acute complications. You can get acute liver problems, you can get a number of problems which require hospitalisation. So that's one aspect of sickle. And during any of those hospitalisations, if you're anaemic or if you -- I should mention the chest crisis where you're sickle in the lungs, and that's -- you get a major respiratory failure.

So for a lot of these acute problems you need urgent blood transfusion, which I'll -- I can come on to in a bit.

So, many sickle patients will have received, at some point in their lives, will have received blood either -- you know, for an emergency indication. That's one side of sickle. Then

obviously the other side of sickle is the chronic disease, the management. So with many years of sickling you can get damage to joints, you need joint replacements, you get damage to the heart, lungs, liver and kidneys, leading to sort of chronic -- chronic organ damage, and all these things will contribute to an early mortality.

MS RICHARDS: You've explained in the report that transfusion in this context can be used to correct anaemia or reduce the proportion of circulating sickle cells.

DR RYAN: Yeah.

MS RICHARDS: So, as I understand it, transfusion is not, in contrast to thalassaemia, the mainstay of treatment, but it is, as a practical reality, something that many people with sickle cell disease will have undergone on more than one occasion?

DR RYAN: Yes.

MS RICHARDS: Often on repeat occasions?

DR RYAN: So for some of the complications -- so we know from a lot of evidence-based studies that it -- if you can predict children who are at risk of stroke -- and we can do that now by

scanning of the major blood vessels leading to the brain, we can actually identify children who are likely to or are particularly at risk of stroke -- we know that if you give them regular blood transfusions you can prevent that stroke happening. So that's the standard of care in the UK for children. They are screened from about the age of two, and if they're at risk of -- felt to be at risk of stroke they're offered transfusions for a period of time.

If you've already had a stroke as a child or an adult, the evidence shows that transfusion is the main treatment to prevent you having a further stroke. So that -- those individuals tend to stay on long-term transfusion programmes. Some patients, you know, have been on it for 20 years now.

The -- we also -- although we have other drugs that we can use to try to help prevent the painful crisis, some of the chest complications, there are number of individuals who have such bad disease in terms of coming into hospital for pain or other problems, that we offer them regular blood transfusions. So, at the moment, we probably have -- somewhere between about

5-10% of all our SS patients are on regular blood transfusions. And by that, typically they have a blood transfusion every four to six weeks sometimes more often, and we do it in the form of exchange blood transfusions. So that's where you take out blood and you put donated blood back in, and that effectively lowers your sickle percentage.

And that's -- those numbers are increasing because our patients are getting older, they're getting lung problems, they're getting other indications. And actually blood transfusion makes them feel -- they don't get pain, you know, they're able to go about their normal lives, so it really -- I think our threshold for giving regular blood transfusions is going down all the time.

MS RICHARDS: In terms of those with sickle cell disease, leaving aside for the moment any question of hepatitis C, what's the life expectancy and how has that changed over the years?

DR RYAN: Well, it's changing all the time. We don't really know because actually until recently we've not had a significant number of

older patients.

We know -- you can project across a group of patients that a study from King's in London showed for such patients a life expectancy maybe of about in the sixties, but that was a group of patients -- and those patients who have the most severe disease are typically living into their forties still.

We have introduced new treatments that we think will impact on children, and ultimately adults, and then we don't know what the impact of regular transfusions is. So I -- if you asked me to estimate, I would say it's in the order of 50s for SS and probably 60s or 70s for the other types of sickle.

So on average, about 20 years, you know, less than comparable peers.

MS RICHARDS: Now, given the amount of blood transfusions that many people with sickle cell disease may have received, would you agree it seems likely that there will have been a number of people with sickle cell who received transfusions prior to the early nineties who would have been infected with hepatitis C as a result?

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DR RYAN: Yes, I would say so. We still have -- we have -- our patterns in the sickle cell in the UK reflect periods of immigration. So we still have a lot of people coming in from Africa and we still see a lot of hepatitis C acquired in other parts of the world, but I'm sure -- I think a lot of the patients who had the chronic hep C prior to the 1990s, I think most of those would be probably dead by now.

In terms of HIV, I've only seen a couple of patients with HIV, even in patients who have had multiple transfusions from east Africa, so I'm quite sure what the incidence would have been in HIV, but certainly hepatitis C, I'm sure, yeah.

MS RICHARDS: And what would be the additional affect of hepatitis C upon an individual who has sickle cell disease?

DR RYAN: Well, I think it would probably compound the risk of developing chronic liver disease. Now chronic liver disease in sickle again can be multi-factorial, it can be related to iron overload from transfusions, it can be related to sickling, damage to the liver itself, so I think it would compound the risk of developing chronic liver disease.

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I also -- so -- but -- but like thalassaemia, if patients have got hepatitis, they are -- they are referred to the -- the liver teams for managing -- managing it. So -- so it would -- again, anaemia, because they're baseline, they're quite anaemic, they would need -- it would compound the anaemia, and they may need the odd transfusion for that.

MS RICHARDS: And as I understand it, there isn't any data as to the numbers of individuals with sickle cell disease who might have been infected through transfusion in the United Kingdom?

DR RYAN: No, no. I mean, I was -- I do remember when we did the look-back exercise in '94, I worked in hospital with a big sickle population and we did -- we did encounter a number of patients who had received blood, but those patients -- I mean, most of those parents would not be living now.

MS RICHARDS: Can I then ask you to deal with -- or ask you to deal with the other rare inherited anaemias and other conditions in which transfusion would be a significant part or mainstay of treatment, please.

DR SEKHAR: So I'll deal with the latter part first.

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We use transfusion a lot in this country for medical and surgical problems, when people need to have blood transfusions either because they're not making enough blood or they're losing blood. So this is different from transfusions that are needed for inherited conditions that we've been talking about so far.

On the whole, the use of red cells is going down in the UK. On the whole, the use of transfusions for surgery is going down in the UK, as compared to transfusions for medical conditions, which is going up.

The use of cryoprecipitate is going up in the UK, and so all of these patterns are basically reflective of a few advances in science and practice and policy. So since 2014, there's been a lot of consciousness about using blood sensibly, and not overusing blood, and that's across the world. It's called the patient blood management philosophy. And that's been hugely promoted everywhere, including UK. So the use of blood has fallen as people have become more conscious that using less blood is actually okay.

There's been very good quality trials since

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the early 2000s to support that. You don't need as much haemoglobin levels to be present in your body through a surgical procedure or even in normal day-to-day life. So previously we would transfuse people so that the haemoglobin levels were around 10, 11, or whatever, and these days we are fairly satisfied with lower levels of haemoglobin. So these have led to improved use of red cells.

In conditions where people have severe bleeding, we also use plasma. So that's FFP. And we use cryoprecipitate. So these two have been the mainstream of treatment in inherited bleeding, historically.

There's still -- plasma is still the mainstay of inherited Factor V deficiency, but otherwise we've moved on to more improved products.

So in people who have severe bleeding, like trauma or burst blood vessels or cardiac surgery or liver transplant, it's commonplace to use a combination of red cells, plasma, cryoprecipitate and platelets.

In actual fact, when somebody donates a bag of blood, all of these are included in one bag

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of blood, but in the UK they are split into separate units, and when people need it they're used in combination of packs. And the number of packs that need to be used over time has changed over time, so we used to use lots of red cells, and quite little of plasma, and there's been lots of very good quality evidence to say that that ratio should reflect real state of blood circulation. So the more blood we use, the more important it is to use a combination of products so that we don't bleed excessively due to lack of plasma.

So these have been the sort of patterns of blood use in the UK in the last decade or so.

In terms of the outcomes of massive bleeding or major haemorrhages, the improved use and improved availability of blood has made a huge difference to survival, and so lots of statistics have shown that the better quality blood replacement early on in a bleeding patient, the better the outcomes are. And in some sections or in some groups of patients, cryoprecipitate has become a very important part of that treatment.

So moving on -- away from patients who

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bleed, there is the group of patients who might be anticipated to bleed. So there's a diagnosis of, say, bowel cancer and that surgery is likely to lose blood, but you have enough time to make up for the blood while waiting for that operation to happen.

So there's lots more emphasis these days on pre-assessment, doing the blood test, treating the anaemia before the surgical procedure is done. So, again, there's been rationalisation of blood use because of improved processes before the operation is done.

The second large group of patients who need blood are people whose bone marrow cannot produce blood. And separate from the inherited diseases are conditions like leukaemia where the disease itself interferes with the bone marrow or the treatment interferes with the bone marrow. And such patients are usually dependent on transfusion until the bone marrow can pick up. So that's usually for a period of two or three or four months while they're on incentive treatment. And the kind of transfusion needs for such a patient would be along the lines of two units a week, of red cells, some platelets

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every so often. And because these are related to the bone marrow, it's not so much affecting of plasma or cryo.

So these patients are in need of what we call cellular products, so red blood corpuscles and platelets.

Historically, we used to base the amount of red cells and platelets on the figures. So the people will have a blood test every day, know what the platelet counts are, and then we base the transfusion.

What's changed in the last 10 years or so is that the thresholds at which we transfuse patients is dropped so it's now considered safe that we don't transfuse at certain level but we transfuse at a much lower level than we used to historically.

So again, there's been quite a lot of rationalisation in terms of blood use. And overall, UK adherence to such policies within the groups I'm alluding to is on the whole very good. There's lots been audits undertaken at individual hospitals, across regions, across the country which reflect more or less continuous improvement in how blood is used.

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In terms of the infectious risk of blood, patients who are identified as needing lots of blood, including patients like sickle cell disease and so on, will be vaccinated for hepatitis B vaccine, and so that's much less a problem.

The -- in late -- in 1999 the UK implemented a procedure called leukodepletion which basically removes all the white blood corpuscles from the donated blood at source. Because in England and Wales the National Blood Service is the main provider of blood, this can be done reliably at source. In other countries where you don't have such a centralised system, people would have to buy the filter to be done at the bedside. So it's very variable.

But in the UK, it's a very systematic process, and so leukodepletion was done primarily because of the worry about vCJD but has had a lot of benefits in many other ways and has reduced both the reactions related to transfusions but also infection risks related to transfusion.

There are a couple of other processes which are available for reducing the infection risk,

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and they're called pathogen inactivation technologies. Some of them are very old, so for example the solvent detergent plasma that's been available for many, many years is one such technology. But in -- for the cellular products there have been some new technologies, and across the world they're variably implemented. The commonest technology is to make platelets safer, and the main worry with platelets is more about bacterial infection rather than viral infection.

So pathogen inactivation of platelets is practised in different countries like Switzerland, Kazakhstan, et cetera, but in this country it was assessed by the SaBTO working group. The existing practice for platelets was thought to be so robust that we don't really need that at the present time.

The red cell safety pathogen inactivation is work in progress, and there's a very good trial that was done in Ghana, along with Professor Aline from Cambridge, who -- and that trial established that malaria risk was much reduced by pathogen inactivating. In this country it's still on a trial basis because,

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again, our products are deemed sufficiently safe.

In terms of inherited --

DR RYAN: For -- the inherited anaemias tend to be managed by the same doctors that manage thalassaemia, because they are conditions where you either don't produce enough red blood cells or you have an abnormal haemoglobin or have a haemolytic anaemia where the red cells are broken down. So they're managed in much the same way with transfusions, as required for symptoms or specific complications, and they have a tendency to load with iron as well.

It should be mentioned that even if you don't have transfusions or you have very infrequent transfusions with both thalassaemias and some of these disorders you can still accumulate significant amounts of iron, because of the way the body reutilises the iron, and still need to take iron chelation drugs.

MS RICHARDS: I'm going to move on next to the primary immunodeficiency disorders, and ask Professor Edgar and Dr Marshall to address that.

Could you tell us again -- perhaps crystallise with some quite complicated science

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and some names that are definitely beyond my skills of pronunciation, and tell us a little bit about PIDs.

PROFESSOR EDGAR: Okay, so primary immunodeficiencies are a group of conditions where one or other or indeed several components of the immune system aren't working properly, and that renders effective people vulnerable to infections.

The first primary immune deficiencies were described in the 1950s, and the number of these conditions has increased exponentially over that time. There are now probably 400 different conditions. And they affect all age ranges, from newborn infants to people in their older age groups.

There's a range of severities. So at the most severe end of the spectrum is a condition called severe combined immune deficiency, where multiple components of the immune system are defective, and that usually presents in the early months of life, and such babies would require bone marrow -- stem cell transplantation.

At the more mild end of the spectrum, some

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people will have an isolated deficiency of an immunoglobulin or antibody molecule which might not even need treatment. But then there's a group of what are called primary antibody deficiencies, which are the -- probably the main group in most of our practices in Europe and the UK, where patients don't make immunoglobulins or antibody molecules effectively, and as a result they're vulnerable particularly to recurrent infections, particularly chest disease, and one of the mainstays of treatment for that group of patients is immunoglobulin replacement, and that's obviously a blood-derived pharmaceutical product.

In terms of numbers of affected people, we have a UK national registry, we have European registries, and at present, there are about 5,000 people in the UK registered as having a primary immune deficiency, although we know the actual number is probably closer to twice that amount. That's because there's incomplete registration of these patient numbers.

And as I say, the most common group of these disorders in the UK would be the primary

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antibody deficiencies.
MS RICHARDS: And as you say, the long-term treatment with blood products has been a cornerstone of treatment for some types of these primary immuno-deficiencies for a number of decades.
PROFESSOR EDGAR: That's correct. Really immunoglobulin replacement therapy was commenced when the first case was reported in the 1950s, of a young boy who had what was called Exlingpayglob(?) anaemia.
The availability of that treatment has developed over the years. In the 1970s and '80s, immunoglobulin was given by intra-muscular injection, which was a very painful process, and which resulted in partial correction of immunoglobulin levels. Because of technological advances then in the 1980s and '90s, intravenous immunoglobulin replacement therapy became available, and that was given by infusion routinely once every three weeks or so for most patients.
Since then there have been developments in terms of giving immunoglobulin by self-administration, usually subcutaneously.

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That's not an injection to the vein but under the skin, usually of the tummy or the thigh, and that can be done by patients independently at home, possibly once a week, that sort of frequency. Those are the main modalities of treatment now.
DR MARSHALL: If I might add, it's worth noting that immunoglobulin is actually widely used now for non-primary immune deficiency conditions. For a number of secondary immune deficiencies which are caused by other problems, such as blood -- or other blood disorders or cancer, but also for neurological conditions, where very high doses of immunoglobulin can be used to prevent inflammation. So the distribution of usage of immunoglobulin now compared to the eighties and nineties is very different, but we've concentrated on the primary antibody deficiencies in all this discussion because that was the group that was treated at the time that this Inquiry is interested in.
PROFESSOR EDGAR: The group that Sara refers to, the secondary antibody deficiencies, that's the fastest area of increase in immunoglobulin use.
MS RICHARDS: I think you said in your report that

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immunoglobulin replacement therapy is a human blood product which consists of immunoglobulin extracted from donated plasma which has been separated from units of blood from thousands of blood donors.
PROFESSOR EDGAR: Yes, that is correct.
MS RICHARDS: And it was first used in the treatment of patients with a primary antibody deficiency in 1952 and in the UK since 1956?
DR MARSHALL: Yes.
PROFESSOR EDGAR: Yes.
MS RICHARDS: And you've observed in your report this: you say this:
"It's always been recognised that there is a risk of the transmission of plasma-borne infectious agents from immunoglobulin replacement therapy. In the review article published in 1957, the panel suggested that no fraction prepared from pooled plasma by any technique be presumed to be free from the virus of homologous serum hepatitis unless shown to be so by volunteer studies or by application of effective sterilising technique."
One of the questions I've been asked to ask by core participants is just to define what that

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term is, homologous serum hepatitis.
DR MARSHALL: That was a term that was used back in the 1950s, and that was just a generic term for serum -- for what we would now call a blood-borne hepatitis, but that just reflects the changes in vocabulary over the time.
MS RICHARDS: You've identified three known outbreaks of hepatitis C infection related to immunoglobulin usage in the United Kingdom. Could you just talk us through those?
DR MARSHALL: Yes, there were a number of -- when intravenous immunoglobulin was -- started to be used, which is in the 1980s, it was noted that there were small groups of patients who presented with either -- acute hepatitis, which could either be attributed to hepatitis B or to what was then called non-A/non-B hepatitis. The largest group was the last one, in 1994, where a cohort of patients, I think it's 36 patients in the UK, but as part of a much larger group of patients in the US, presented with acute hepatitis in the weeks after having a very specific batch of immunoglobulin.
We know quite a lot about that episode because it was very -- studied in great deal at

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the time. And what we know is that because of the way the patients were being monitored -- at that time in the UK it was standard to have liver function tests every six weeks, and we know that patients presented with -- there were three patients who presented with a blip, a slight increase in their liver function tests within weeks of getting this particular batch.

What that led the doctors at the time to do was a look-back to see what these patients had in common, and it was identified that they had all received immunoglobulin from a specific manufacturer, and that they all then -- when they went back in more detail, they could see that it came from a specific batch.

So that was a very defined episode. They were all -- all the affected patients were then shown to have the same hepatitis genotype, so it was all tracked back. And that's been the biggest episode that's been described, and we've learnt quite a lot about hepatitis C in this group through the study of that group of patients.

MS RICHARDS: And you've said in the report in relation to that 1994 outbreak, 29 of the

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patients who received this particular product from Baxter Pharmaceutical were found to be hepatitis C positive on two or more occasions.

DR MARSHALL: That's correct. And they have subsequently been -- they have been followed up -- shall I talk a little bit about the natural history of --

MS RICHARDS: Yes, please.

DR MARSHALL: So in the UK only, there were 36, I think, patients identified as being exposed, of whom 29 had a positive test on more than two occasions. When they look at that cohort of patients five years later, they found that 25% of the patients had either got end-stage liver disease or had died with associated liver disease. So much more rapid progression of disease than would be expected in a group of patients with a normal immune system.

I think that people had always recognised that this group of patients was particularly susceptible because their immune system doesn't work very well. But this kind of gave us a measure of just how aggressive hepatitis C could be in this group.

MS RICHARDS: Just the two earlier outbreaks that

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you described in your report, one was in 1983.

DR MARSHALL: Yes.

MS RICHARDS: And you've said a British-produced plasma product was implicated, and then the second occurred in relation to Scottish product in Scottish patients.

DR MARSHALL: That's correct.

MS RICHARDS: Do you remember the date of that second one?

DR MARSHALL: I can give it to you but it's not on the top of my head.

MS RICHARDS: Thank you. Because the report doesn't say.

DR MARSHALL: No.

MS RICHARDS: We have a footnote which gives us the date of a paper which may -- (overspeaking)

DR MARSHALL: No, I can give you that.

MS RICHARDS: And do you know, again, off the top of your head -- don't worry if you don't -- the numbers, other than it was less than --

DR MARSHALL: Small. Well, it was a small -- I think it was less than ten in each case.

MS RICHARDS: And has there been any long-term follow-up that you're aware of in relation to either of those two cohorts?

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DR MARSHALL: There has been no systematic follow-up of those two cohorts. Partly because at the time, it was very difficult to identify the non-A non-B, it was hard to see them as a cohort because there wasn't the same discipline -- sorry?

PROFESSOR EDGAR: And the testing wasn't available.

DR MARSHALL: And the testing wasn't available.

MS RICHARDS: And this was at some point in the 80s?

DR MARSHALL: Yes.

MS RICHARDS: What's then -- are there any differences in terms of either natural history diagnosis and treatment of hepatitis in individuals with primary immune deficiencies?

DR MARSHALL: Yes. I mean in terms of the natural history, I've already alluded to the fact that this group of patients has particularly aggressive disease, presents much earlier than we would expect. More people develop more severe disease more quickly, to answer that first question about natural history.

In terms of diagnosis, because these patients don't make antibody, that's why they're having the immunoglobulin, all the standard antibody-based tests that we would do in

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patients with a normal immune system don't work. And so the normal immuno assays that we were talking about before, or on Wednesday, are not applicable in this patient group, and that means that in those early episodes one might miss -- one might get a falsely negative result because you were using the wrong tests.

Once viral load and the PCR-based tests came in, those were the tests that can be used in this patient group, and those are the tests that we continue to use in this patient group. So there is a difference in diagnosis.

In terms of treatment, the patients affected in the 1993/4 episode, some of them received interferon, and some of them subsequently received interferon ribavirin.

Not enough to be able to give a definitive "they do better" or "they do worse", but we do know that in terms of transplantation this is a patient group who often have other infectious complications because of the nature of their problem.

And if you have a chronic infection of any type and undergo a transplant, you're much more likely that that infection will get worse and

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that may be life threatening.

So the opportunity for transplantation is not always available for this patient group.

MS RICHARDS: And then were you able to find any reference to HIV being transmitted to this particular category of patients --

DR MARSHALL: That's a very good question, and in fact there are no reported cases of HIV associated with immunoglobulin contamination in the literature. And the reason for that is probably because HIV is a retrovirus, it's a different kind of virus to hepatitis C, and it appears that the manufacturing process, the standard first step of the manufacturing process in the preparation of immunoglobulin destroys the wall of the HIV, and so in fact kills the virus.

MS RICHARDS: There are two methods you described of immunoglobulin being administered, intra-muscular and intravenous, and I understand there's a difference in terms of infection with hepatitis through those two routes.

DR MARSHALL: Yeah, which is very interesting.

Intramuscular immunoglobulin was standard practice until the 1980s, and intramuscular

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immunoglobulin does not appear to transmit hepatitis C. In contrast, intravenous immunoglobulin has been shown to. Subcutaneous immunoglobulin, which David referred to earlier, which is a often-used form of immunoglobulin now, has not been shown to transmit it but may do.

Quite why immunoglobulin intramuscular immunoglobulin doesn't and intravenous immunoglobulin does is not completely clear. It may be because the preparations are different, it may be other subtle differences in the way the immune system that is there responds to clearing the virus.

MS RICHARDS: And as I understand it, the reason why intramuscular immunoglobulin is no longer the favoured method of treatment is not because of issues in relation to transmission of hepatitis.

DR MARSHALL: No.

MS RICHARDS: But because it's -- as you were describing, Professor, it's a more painful and problematic --

PROFESSOR EDGAR: And less effective. You don't achieve the same sort of plasma levels that you want to.

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MS RICHARDS: Can you assist with this: what, if any, steps are you aware of that were put in place to try to identify patients affected by viral contaminated immunoglobulin?

DR MARSHALL: Well, I think I might answer that question by describing the steps that were put in place to -- rather than doing the look-back, but in -- prospectively. When patients are started on immunoglobulin -- I'll describe what happens now and then go back.

When patients are started on immunoglobulin now, first of all one would take their consent and advise patients about the risks of -- the theoretical risk of HIV, of hepatitis B, hepatitis C, variant CJD, and also unknown viruses that we -- and other infectious agents that we don't know about.

We would always screen patients for whether or not they had hepatitis or HIV before giving them treatment. And we would then -- and test their liver function test as a routine. Patients then undergo regular testing for their liver function every three months, once they start on treatment. And then, once a year, they would, in most centres, or many centres, would

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have blood stored, so that if problems arise in the future, one can then look back and get an idea of when they may have been infected.

Now those -- there are a few other steps that were taken. One is to restrict the product -- there are a number of different immunoglobulin products available, and patients, once they were stable on one product, would stay on that product rather than mix and match with many different products. And the idea behind that was to minimise the risk: if you're only having one product, and preferably only having a limited number of batches of that product, your risk is limited.

Those steps were put in place in around the 1990s. There was a document, which was called the Consensus Document on the Diagnosis and Treatment of Primary Antibody Deficiencies, which was a very influential document, and this laid out exactly what the standard of care was. And in the UK, most of the centres really adhered to that, and these steps were all laid out in that document.

MS RICHARDS: And that was 1994?

DR MARSHALL: That was 1994. 1994/5.

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MS RICHARDS: You say in your report that since the 1994 outbreak that you've described, there has not, as far as it's known, been any further immunoglobulin-associated viral contamination.

DR MARSHALL: In the UK.

MS RICHARDS: In the UK.

PROFESSOR EDGAR: Yes.

DR MARSHALL: Correct.

MS RICHARDS: And that, as I understand, has led to some ongoing discussions about whether you still need to keep samples frozen and whether you still need to have annual screening.

PROFESSOR EDGAR: That's correct, yes. I mean, the steps that Sara has described are widely practised but there is now a bit of a debate as to whether we really need to do all of them because the improvements in product manufacturing processes and the length of time since there's ever been a problem is leading people to kind of challenge that a little bit.

MS RICHARDS: And then can I just go back to something you said a few moments ago, Dr Marshall, which was about the consent process.

Notwithstanding the lack of any further

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outbreaks or episodes, as far as you and your colleagues are aware, since 1994, patients will nonetheless be advised, as part of the obtaining of consent process, about the risk of viral contamination?

DR MARSHALL: Yes, yes.

MS RICHARDS: Including hepatitis B, C?

DR MARSHALL: Yes.

MS RICHARDS: Including HIV?

DR MARSHALL: Yes.

PROFESSOR EDGAR: Yes.

MS RICHARDS: What about the possible exposure to vCJD?

PROFESSOR EDGAR: Yes.

DR MARSHALL: Yes.

MS RICHARDS: So that's all part of it --

DR MARSHALL: So there are five -- there are the five, which is HIV, hepatitis B, hepatitis C -- and now I'm going to forget them -- variant CJD, and the unknowns.

PROFESSOR EDGAR: And the unknowns, yes.

MS RICHARDS: So they're told that.

PROFESSOR EDGAR: Yes.

MS RICHARDS: Will the nature of those risks typically be discussed with them?

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PROFESSOR EDGAR: Yes. I mean, typically people will be told that there is a risk of getting these viral infections, that these infections can be very severe, but that will be tempered -- I mean, in this day and age -- you know, in -- at this time we would be saying: it has been a long time, 25 years, since anyone has ever got it through this route.

But there are a lot of unknowns, particularly around variant CJD and the viruses we don't know about. And so that would be alluded to. And patients are usually given information sheets so they can take them home and read them again, because the context of a clinic space is not always the best place.

So we do always give written material as well, that says that.

MS RICHARDS: And would the standard practice be to obtain written consent before undergoing immunoglobulin treatment?

DR MARSHALL: Yes.

PROFESSOR EDGAR: Yes.

It's possibly also worthwhile commenting that this doesn't all happen in one consultation, because usually when you're seeing

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somebody and considering immunoglobulin replacement therapy, that will be over a period of time, and there will be information given over several appointments, and it's often put in the context of a risk/benefit analysis. The benefit is -- proposed benefit of immunoglobulin replacement will be to reduce the number of infections the patient is suffering and increase their overall wellbeing, whereas the -- the potential risk is this theoretical risk of viral transmission, and we will specifically say to people there has not been an outbreak in the UK with these products since 1994 and we know that these products have not transmitted these viruses in all that time, but we can't rule out that there will be a new class of viruses in the future that we don't know about. So it's putting it in that risk/benefit context.

MS RICHARDS: Then last question before the break, sir.

Do you think that there may be undiagnosed patients, so patients with primary immunodeficiency disorders who received immunoglobulin replacement therapy in the periods with which we're talking about who may

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be infected with hepatitis B or C and be unaware of that? Or be unknown to clinical services?

DR MARSHALL: Yes. I spent a little bit of time thinking about this, as to whether there were infected patients out there who we didn't know about. Patients who are on immunoglobulin because of primary immune deficiencies will generally have severe disease, and it's very unlikely that they will not be under the care of specialist services once they have joined a specialist service. And I think that given that the -- the standard of care that I've just discussed, of regular testing for hepatitis C, even in the absence of any known outbreak, means that I think it is very unlikely that we have patients who are currently in the UK with a primary immune deficiency who are not -- who were infected in the 80s and 90s who are not known to services.

PROFESSOR EDGAR: Yes, I would agree.

MS RICHARDS: And that --

DR SEKHAR: It is worth perhaps commenting about the last aspect of the conversation here, which is -- so this -- this question of informing people about the risks of any blood product is

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-- is meant to be across the groups of all transfusion recipients, and the SaBTO guidance specifies what and how. The opportunities to do that is different in different settings, and so the compliance with it varies.

MS RICHARDS: And it's an issue to which the Inquiry will undoubtedly be returning in the future, I've no doubt on more than one occasion.

Sir, that completes my questions but I'm conscious core participants may well have questions they want me to ask the panel, so this may well be the ideal moment.

SIR BRIAN LANGSTAFF: One way we could manage this is perhaps allowing you ten minutes. You may think you want half an hour but if you want ten minutes then we can take a short 10-minute break, allow that to be done, and then the final few words that have to be said will be -- will be said. And final few questions asked.

MS RICHARDS: Very happy with that, sir.

SIR BRIAN LANGSTAFF: So let's take ten minutes now and there will be coffee or tea available when we finish, which won't be long after that.

(3.04 pm)

(A short break)

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(3.19 pm)

MS RICHARDS: Sir, there are a handful of questions that core participants have asked me to ask. They're primarily, I think, going to be relevant to Dr Tunstall and Dr Gooding's areas of expertise because they're in the context of bleeding disorders for most part.

The first is, in relation to gene therapy we talked about current treatments and developments but in fact I didn't ask you about gene therapy and what might be happening in that regard.

Are you able to assist?

DR TUNSTALL: Certainly.

So gene therapy is an area of very active research in haemophilia at the moment, and there have been some very encouraging studies in both haemophilia and haemophilia -- haemophilia A and haemophilia B, with stable levels, or -- or stable-ish levels of expression which are coming out for some years.

We haven't yet seen a movement into a commercial market, it's certainly in the place of research projects at present. And we don't know if that response will be sustained indefinitely or whether it will be something

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that will be there for a number of years and then wane from there.

So it's certainly something on the horizon. How swiftly it moves from being on the horizon to everyday practice, I don't think we know yet.

There were particular barriers for children with the current technologies in that it wouldn't be predicted to work in children due to liver cell turnover, at present.

MS RICHARDS: And the aim of the gene therapy that's the subject of the research you refer to is to have higher lifelong levels of factor? Is that right?

DR TUNSTALL: I guess potentially lifelong, although whether, you know -- a decade or more might be something to look at, yeah.

DR RYAN: Can I add that gene therapy looks very promising for thalassaemia, and in fact NICE are considering the use of commissioning of gene therapy in a few months' time for certain groups patients, and the data suggests that gene therapy gives the vast majority of patients -- they become transfusion independent. So it's actually a very promising treatment for thalassaemia, and it's under trial for sickle,

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where, again, it looks very promising as well.

MS RICHARDS: The next question again relating to the treatment for bleeding disorders. Is it correct that very recently, so this month, a decision has been made, at least in relation to England, not to fund recombinant treatment for VWD and Factor VIII deficiency?

DR TUNSTALL: I'm not aware what is in the public domain or not, for that.

MS RICHARDS: Well, it's sufficiently in the public domain that somebody has given it to me as a question to ask.

I am told, and I have no knowledge myself of this, that NHS England has made a decision not to fund recombinant treatment for people with VWD or Factor VIII deficiency.

DR TUNSTALL: I believe that the case, yes.

MS RICHARDS: So that will leave those particular deficiencies reliant in part upon plasma-based treatment, although there's obviously also in relation to VWD -- DDAVP, as we've already discussed?

DR TUNSTALL: Yes.

DR GOODING: Yes.

MS RICHARDS: Then the -- there's a question, I'm

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not sure whether you would be able to answer this but I'm going to ask you and see. So it's -- the position of people with haemophilia infected with HIV and/or hepatitis C, are there any concerns that anti-depressants have had any particular detrimental effect or created side effects for that cohort?

DR GOODING: In theory there is a potential acquired platelet dysfunction sort of element to some anti-depressants, but whether it's a significant affect in terms of haemophilia outcome, I'm not sure. I know I would say that it's not something that we would -- I think the -- the caveat with prescribing anti-depressants for people with bleeding disorders is that they would be used with caution, and typically I think if -- if you were to see a side effect like that, you'd -- you would pick up on it fairly quickly. It tends to manifest itself with easy bruisability.

DR TUNSTALL: Is that a question specifically about antiviral drugs?

MS RICHARDS: I'm afraid I don't know. The question is the question I read out.

DR TUNSTALL: So I would agree with Richard about

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that aspect but I don't know about the question with -- specifically.

MS RICHARDS: The next question I'm asked to ask you is about the assays, so going back to the question of diagnosis, when it's appropriate to use stage 1 assay and when stage 2 assay?

DR TUNSTALL: So from -- there's basically two different ways of doing a Factor VIII assay, and they usually give a very consistent results. There is sometimes a discrepancy with certain abnormalities in the Factor VIII gene that there is a discrepancy. It's not usually a case of being entirely normal on one case and -- and it showing, say, severe haemophilia the other way. It's usually the baseline level changes, or what we would consider the functional level. So it is our practice -- we consider it best practice for anyone with a diagnosis of haemophilia to do a two-stage or chromogenic assay.

There are also situations where, for monitoring therapy, a chromogenic or two-stage assay is more appropriate.

MS RICHARDS: Again, I'm afraid with the two of you, how does the severity of a person's haemophilia affect the advice you would give them about the

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activities they should avoid?
DR GOODING: I suppose it depends on their -- it's a very individualised sort of decision, that, I think. You may advise people with a bit of -- a more severe condition that they can participate in certain activities when they feel that their treatments -- say they're on prophylaxis, that would render them safer perhaps, than perhaps someone who is a more severe-moderate sort of -- I was going to say, it needs to be very carefully tailored to -- to the patient and what you think their risk is, and -- and also their bleeding phenotype, so not just the -- the numerical levels but actually how they are themselves. And then the advice then is -- is a negotiation, I suppose, about risk. And I think this -- it's all about trying to present information to a patient and their family about, you know, how much they want to do something and what the risks of that might be and whether they're happy to accept those risks and if there is anything we can do to modify those risks to enable people.

So that's the sort of context, I think, of that sort of advice. It's not as simple as, you

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know, just numbers.
MS RICHARDS: Then there's a specific haemophilia B related question, what is leiden haemophilia B, and what treatment would sufferers be expected to receive, and why?
DR TUNSTALL: So that's -- I mean, it's one case where we really do see dramatic differences in -- in factor levels, with factor B leiden, and we would often see a normalisation or much higher Factor IX levels post-puberty, and so sometimes it's to the extent that you will have -- you see boys with moderate haemophilia B who -- who may be severely enough affected to require prophylaxis but then the levels rise with puberty and they may never need to administer treatment again.
MS RICHARDS: In severe haemophilia what's the average Factor VIII level you would aim to achieve? So in severe haemophilia A? Is there an average Factor VIII level you aim to achieve?
DR TUNSTALL: It depends on the context, and when we're saying -- if we're talking about prophylaxis or if we're talking -- covering for surgery, so -- so these, or -- or after a bleed, and all of these things will be different

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situations, if we're talking about prophylaxis, we generally don't aim so much on peaks and more on the troughs. So we try to preserve a level. I think most of us are unhappy with a trough that is less than 1 and much happier if the trough is above 3. We may, you know, personally be happier if the trough is 10, but there's limitations of cost and technologies in achieving that.

We don't really know about peaks and prophylaxis, how important they are. So it's less about aiming for a peak and more about sustaining a process level.
DR GOODING: And, again, having a clinical response to the number of bleeds that you're seeing and the symptomatic joint problems at the same time.
MS RICHARDS: And on the topic of prophylactic treatment, is the aim to preserve joints or prevent joint damage, preserve life, or both?
DR TUNSTALL: Preserve life as in prevent death or --
MS RICHARDS: I'm assuming that's -- I think that's what lies behind the question, yes.
DR TUNSTALL: I mean, obviously, both. But we know, you know, if we have adequate levels to prevent

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joint damage, then that's going to dramatically reduce the risk of life-threatening bleeding.
MS RICHARDS: Then two slightly broader questions. Again it may be that the panel's able to answer them or not, or that we need to direct them elsewhere. The first is, does hepatitis infection cause immunodeficiency?
PROFESSOR EDGAR: It doesn't cause primary immunodeficiency, but chronic illness can, by its nature, cause a degree of immunodeficiency.

Would you agree with that?
DR MARSHALL: I'd agree with that.
MS RICHARDS: Very final question, what pathogens are thought to be transmitted through blood products in the United Kingdom now?

And if you don't feel able to answer that, that's fine, but if you do, please do.
DR SEKHAR: We usually counsel for the five that Sara eluded to, but every so often the Blood Service will screen for lots of contemporary ones, so that list changes from time to time.
MS RICHARDS: Okay. Thank you. Those are the questions. I'm just going to turn my back to see if there is anything vital and pressing?

No, I'm happy to say not.

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SIR BRIAN LANGSTAFF: Well, that was indeed the last question because I have none of my own.

It just remains for me to thank you hugely for coming to give your time and your evidence to us. It may have seemed to each pair of you that there have been a form of selective silence at times because of the way in which you have your own particular specialties, but I hope you see how they all fit together and how it was useful for us to present you as a panel dealing with the different conditions that you've dealt with and informed us about so beautifully.

So thank you very much.

[Applause]

Now you have something to deal with, I think, but it doesn't require our experts to stay.

You're very welcome to stay where you are, perfectly happy, but you may prefer to sit elsewhere, you may prefer to go. It's entirely up to you.

Ms Richards?

MS RICHARDS: Yes, sir. So I mentioned on Monday that we had directed some questions to those responsible for decisions about NHS services in

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the four parts of the United Kingdom. And I'm just going to summarise and read shortly from some of the responses that were received.

So we asked a slightly wider range of questions than I'm going deal with now.

The first category of questions I'm going to deal with are about hepatitis C, and we asked two questions that I'm going to describe:

What scans, blood tests and/or other checks and/or monitoring are or should be offered to a person who's been diagnosed with hepatitis C? How often, and over what period of time is the first question asked.

And the second:

Following successful treatment such that the person has received a sustained virological response, what follow-up scans, blood tests and/or other checks or monitoring are or should be offered, how often, and over what period of time?

So we asked about the current clinical practice or what should be the current clinical practice and availability of care in that regard.

I'm just going to read briefly what the four

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responses were from the four parts of the UK, because we know the from the individual evidence we've heard that, on the ground, people have not had necessarily a consistent answer from their own treating hospitals and trusts.

So the response in relation to Scotland -- we had several witness statements from Scotland. These will be published on the Inquiry website hopefully later today if not earlier next week.

On this particular issue, in fact, the Scottish Government asked Professor Dillon, whom you heard from as part of the evidence this week, to provide a response, and the response was this. So in response to the question about scans, blood tests and other checks, he said this:

"These have changed and continued to change radically and are continually updated in national and international guidelines as new evidence emerges. In summary, a person diagnosed with hepatitis C should have either bloods, liver function tests and full blood count, to calculate an FIB4 score or other estimate of fibrosis or an imaging-based estimate, eg fibroscan, to stage their disease.

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Those who don't have evidence of cirrhosis may be treated and a blood test obtained at 12 or 24 weeks post treatment to confirm success and then discharged. Those with evidence of cirrhosis should be treated and remain under six-monthly review to screen for complication of cirrhosis, in particular hepatocellular carcinoma with six-monthly hepatic ultrasounds and estimations of alpha-theta protein and gastrointestinal varices, three-yearly upper gastrointestinal endoscopy."

Then in response to the question about context and monitoring following SVR, effectively already answered, but he said this:

"Again, this area has changed considerably due to the development of the evidence base, especially around the confidence that SVR is a marker of HCV cure, thus the need for long term follow-up has been removed for most patients. As described above, follow up depends on the degree of liver damage, those with cirrhosis needing follow-up."

Of course, we had a slight amplification of that in the course of his evidence this week.

The position in relation to Wales is set out

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in a statement from Professor Chris Jones, the Deputy Chief Medical Officer, and he said this:

"It depends somewhat on the patient's circumstances and choice. In general, where possible the following pathway is followed. Baseline blood tests including urea and electrolytes, liver function tests, estimated glomerular filtration rate, international normalised ration, full blood count, viral load, genotype and fibroscan performed in a one stop clinic. Review patient with results, two to four weeks for with results, and medication ordered according to results, treatment commenced two weeks later, delivery time two weeks. Review patient early in the course of treatment, two to three weeks after starting, to check patient is tolerating treatment, compliance, repeat routine bloods. Further follow-up at the discretion of the treating clinician in partnership with the patient. Review patient 12 weeks after treatment has finished for blood tests to confirm success of treatment."

Then in relation to subsequent follow-up post-SVR, he said this:

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"This depends on the patient's level of disease prior to treatment. If the patient has no or minimal damage to the liver prior to treatment, then the patient is discharged back into the community as no follow-up is required. If the patient has advanced liver disease then they would be followed up appropriately by that service, ie, regular scans for hepatocellular carcinoma and regular monitoring with hepatology. Further later date, blood-borne virus testing is also recommended if a patient continues to engage injecting drug use."

That last part is not for present purposes.

That was in relation to Wales. Insofar as Northern Ireland is concerned, we have a statement from the Director of Surgery and Specialist Services at Belfast Health and Social Care Trust, Caroline Leonard, and what she has said is this:

"The hepatology team in Belfast Trust advise that all new patients with a diagnosis of HCV are offered blood tests [and she's listed the various tests], an ultrasound scan and a fibroscan. Those who have chronic hepatitis C and who are fit for treatment are offered

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treatment. If treatment is commenced, blood tests are carried out during treatment to ensure liver tests remain satisfactory. At the end of treatment, hepatitis C status is checked with HCV PCR test and again three months after completion of treatment. If the PCR test is negative at end of treatment and three months post-treatment, this indicates successful clearance of the HCV infection. In previous years, it was also the practice of the regional hepatology team at the Royal Victoria Hospital to do a check-up PCR test one year post-treatment. In keeping with practice throughout the UK, this is no longer required."

Then in terms of follow-up post-SVR, she says this:

"The hepatology team in Belfast Trust advise that patients who are PCR negative after treatment and who have a normal fibroscan are discharged from the hepatology clinic. Those who have an indeterminate fibroscan result will usually have a follow-up fibroscan at least six months after finishing treatment. If the fibroscan is satisfactory, the patients are discharged. Patients who have a fibroscan

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suggestive of advanced fibrosis or cirrhosis are kept under long-term review at the liver clinic. These patients require an ultrasound and blood test for alpha theta protein every six months to screen for hepatocellular cancer. In addition, such patients have a six-monthly clinic review."

Then to complete the geographical picture, in relation to England we have a statement of Claire Forman on behalf of NHS England. Her statement is rather lengthier, so I'm not going to read out all of it. She refers to what would be the ordinary pattern of HCV care and then on the issue of what happens post-SVR, she says this:

"It's generally recommended that in the absence of liver cirrhosis, patients with HCV who have cleared the virus with treatment can be discharged from follow-up and no routine surveillance is indicated. Many clinicians perform a single repeat check of HCV RNA status and liver function six to twelve months after treatment to identify the very rare patients who suffer a late relapse, but in the absence of co-morbidities, no follow-up is indicated. For patients with cirrhosis, standard follow-up

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post-therapy should include a review every six months with an assessment of liver function by blood tests, including a full blood count, liver function tests and usually clotting assessment. A liver cancer screen should be performed with an ultrasound scan and an alpha theta protein assessment."

Then there's a reference to differential follow-up depending upon co-morbidities.

So the purpose of highlighting those statements, and drawing attention to the fact that they'll be published upon the Inquiry's website is precisely because we have heard people relaying that they have not been receiving follow-up care, and whilst obviously the Inquiry is not in a position to investigate such individual cases, it's hoped that by asking the question of the four nations or parts of the United Kingdom and getting these answers, individuals who feel they have not been receiving the follow-up care that they may be entitled to can use this information to go to their treating clinicians or to their GP and ask to have fibroscans, blood tests and the appropriate referrals.

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That was the first part of the questions we asked. The second was about psychological counselling and availability or non-availability of psychological counselling. I will start, for reasons that may become apparent, with Wales. Again, the statement of Professor Jones, the Deputy Chief Medical Officer. I should say, these are answers to questions that were asked partly about the availability of psychological services generally, and then specifically about the availability of psychological services for those infected with hepatitis or HIV through infected blood or blood products.

The Inquiry in particular drew the attention of those to whom the request was directed to a fund set up in relation to the provision for physical and mental well-being for victims of the Grenfell disaster and asked if there were any similar arrangements to those infected as a result of blood or blood products. This is the position as we understand it to be, or as we are told it is going to be, in Wales.

Professor John says this:

"Psychological support is provided specifically for beneficiaries of the Welsh

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Infected Blood Support Scheme through funding provided by the Welsh Government. The Minister announced the provision of this service in March 2019. The Welsh Government, WIBSS and (reading) trust which hosts WIBSS, and stakeholders, work together to produce a blueprint for the psychological services that are required to meet the needs of those infected and/or affected together with their families. A proposal was taken to the WIBSS governance group and approved. The WIBSS psychological support service began seeing beneficiaries and family members in December 2019. The service is continuing to develop its standard operating procedures, referral process, et cetera. All patients who had previously requested such support were contacted and informed about the service. Those beneficiaries or family members deemed to be at high risk were seen as priority by either the consultant psychologist or lead counsellor."

Then there's a reference to positive feedback.

Then:

"This information is provided from the WIBSS

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website:

"A psychology team specifically for the service has been established. From January 2020, individuals registered with WIBSS, their family members and bereaved family members, can access psychological assessment and treatment concerning the emotional difficulties of being given and living with a diagnosis of hepatitis C and/or HIV. The team are aware of the historical context, and have experience of working with the emotional difficulties that have occurred as a result. The hope is that by offering a specialist psychology service there will be some acknowledgment and recognition of the physical and psychological complexity and impact on the quality of life and relationships."

So there was a very recently established specialist service for those with whom this Inquiry is concerned, that has just been set up in Wales.

Insofar as Northern Ireland is concerned, we again have several statements that will all be published, but the only one I'm going to refer to is again from Caroline Leonard at the Belfast

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Health and Social Care Trust. She says this:

"Prior to January 2019, no dedicated psychology service was available to either the infected or affected patients or relatives associated with the Infected Blood Inquiry. The trust established a working group in September 2018 to consider the implications of Infected Blood Inquiry work as this relates to Northern Ireland.

"At an early stage the working group identified a requirement for additional psychological support specifically in respect of the needs of those people in Northern Ireland directly impacted as a consequence of infected blood products. A funding proposal was submitted to the Department of Health and non-recurrent resources were made available for the Belfast Trust to put in place dedicated clinical psychological capacity to meet these needs. A full time band 8A specialist clinical psychologist is currently funded until the end of March 2021. It's anticipated that further recurrent funding to support this service will be considered in due course. The specialist clinical psychologist provides assessment,

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psychological therapies, liaison and signposting as appropriate for HIV, HBV and HCV infected and affected patients and relatives since January 2019."

And she provides a little further information.

So again, insofar as Northern Ireland is concerned, it appears that there is some form of specialist service (established a little longer than the Welsh service, but still relatively new) but specialist focused upon those who have been infected and affected through blood or blood products.

SIR BRIAN LANGSTAFF: But not specifically mentioning the bereaved?

MS RICHARDS: Sir, the statement, I think -- infected or affected patients and relatives are referred to in the witness statement.

SIR BRIAN LANGSTAFF: Thank you.

MS RICHARDS: So, yes, it does appear to be broader than infected individuals themselves.

The position in Scotland is set out in a witness statement from Samantha Baker. It's quite a detailed statement, and so I'm going try and summarise it. I hope I'll do so in a way

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that doesn't do any injustice to it.

So she explains in some detail that those infected and affected by infected blood and blood products can access a range of psychological support and treatment generally as can other individuals within Scotland. So there's the general provision of psychological services as opposed to specialist provision.

In response to the question that was asked about whether there was any kind of specialist service or anything equivalent to the steps taken in relation to those affected by the Grenfell Tower fire, the answer was that there's no directly equivalent services in Scotland for people infected or affected in consequence of infected blood or blood products, and she sets out some reasons in that respect which I won't read, but others will be able to read on the website.

She does say that as well as the general services that can be accessed through NHS boards in Scotland, there is a haemophilia psychological support service available for patients with bleeding disorders and their family members. It's said that that was

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initially only available to patients in the Edinburgh Haemophilia Centre but has been available to patients and family members across all of Scotland since 2018. It's staffed by one full-time psychologist and a part-time psychiatrist. They're based in Edinburgh but travel on certain days to other Scottish locations. It's available to all those with bleeding disorders and their families, but she says a significant proportion of those using it are infected or family members of someone infected with hepatitis C and/or HIV but obviously that's a bleeding disorder-specific service that sits within the Haemophilia Centre.

Then finally, the position in relation to England is again set out in the witness statement of Claire Foreman on behalf of NHS England.

Again, she points to the availability of general psychological services that might be available to all members of the community and not specific to the communities with which we're concerned. She says that:

"Many patients requiring specialised services for a disease or condition will have

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psychological support needs at some point in their care or treatment pathway, and responding to psychological support needs can be an important part of a patient's overall care package. Whilst it's not expected or desirable for each specialised service to have their own dedicated psychological support service it's expected that all services have in place the necessary links and referral pathways."

So that's a means of accessing either general psychological services potentially or psychological services that might sit within certain areas of medical practice but not specifically for infected blood or blood product recipients.

Then in response to the question about Grenfell Tower service, well, I'll read out the question that was asked and then the answer. The question that was asked was this:

"The Inquiry understands that (a) in October 2018 NHS England announced funding of up to £50 million for a new screening service to be put in place to provide long-term support and treatment for people with physical and mental health issues following the Grenfell Tower fire,

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and (b) a free and confidential NHS service, the Grenfell Health and Wellbeing Service, is available to children and adults affected by the Grenfell Tower fire. Please confirm whether there is any equivalent or similar service in England for people infected or affected in consequence of infected blood or blood products."

The short answer to the question is that there isn't any such service in England. There's a longer answer which in fairness to Ms Foreman is a reasoned answer that's set out in the statement. I'm not going to read all of it out. She talks about NHS England's response to Grenfell Tower being part of its emergency preparedness, resilience and response duties under the Civil Contingencies Act and then she says this:

"In the case of Grenfell and other incidents that year, local communities witnessed extreme events likely to result in significant mental health issues as well as other health problems. In recognition of this, NHS England issued advice to health services about caring for affected people shortly after the incidents.

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This advice encouraged greater vigilance in the healthcare professionals who provided a leaflet. Individuals were signposted to use NHS Choices. As the Inquiry has noted, NHS England announced on 9th October 2018 the services it would put in place for the local community affected by the Grenfell Tower fire. These additional arrangements were made as part of NHS England's major incident response in enabling the NHS to return to normal as part of the recovery phase, and in response to prevent future deaths report made by the coroner."

She refers to a coroner's report in relation to the Grenfell fire which noted that many of those affected by the incident suffered emotional trauma and harm and were therefore likely to need appropriate mental health support, and then says this:

"Whilst services for mental health, including post-traumatic stress disorder and respiratory conditions, are generally available via the NHS for all patients, the services put in place for Grenfell were therefore in response to the specific and additional needs of the Grenfell community. This was consistent with

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the principle that NHS patients with equal need should have equal ability to access services regardless of how those needs arose. In the same way, ill patients with hepatitis C have been able to access NHS services and treatments on the basis of need rather than differentially based on how those needs arose."

Then she refers to both general and more tailored psychological services being in place for individuals affected by diseases generally through existing networks.

So that's the response in relation to England and, as I say, those materials will be published on the Inquiry website if not today, then early next week.

SIR BRIAN LANGSTAFF: Thank you, Ms Richards.

This is the time when I have previously and I will again reflect on the session of evidence that has just finished and look forward to what comes next. So first, reflection.

You may think it follows on, perhaps, a little from what's just been said. Last November, at the close of the first set of hearings during which individuals who have been infected and affected told their stories, I drew

together some of the themes that have been explored and, in particular, I said this and I make no apology for repeating it now:

"A repeated theme has been the often and unanswered call for help and psychological support for those suddenly facing what has seemed an unfair death sentence with all its side effects on partners, friends and family, or the gruelling courses of treatment they have undergone with their own side effects. It is appropriate, therefore, that when we begin our next set of hearings" -- remember, I was talking then last November, so that's these hearings we've now just finished -- "we shall hear in particular from experts on psychosocial and psychological impact as well as from experts on hepatitis, HIV, blood and bleeding disorders. This evidence will help place what we have already heard in a wider context, and prepare for the hearings with decision-makers which will follow."

There can be no doubt, let me repeat that, no doubt, that what we have heard this week has underlined that message, written it in bold, set it out again in starkest clarity. It's done

more than that. It's added the voices of those who spoke via the intermediaries we heard on Monday and putting those voices together with the near 200 or who spoke last year directly to those who are here, or watching online, more than 250 testimonies have emphasised the need for the message about psychological support to be heard.

I can tell you that I have now read over four times that number of written statements, which have in their own individual ways, added to the force of what has been said orally. But what makes me raise this again in such strong terms as I do now is that we have now heard that scientific expertise of the highest standing fully supports that view.

We shall all take our own messages from this week of evidence, but what I personally would like to highlight is this: it must be the case that anyone who has given a life threatening diagnosis may need support and should be offered it, and so too their families may need support.

Yet the very fact that number of people with chronic hepatitis B or chronic hepatitis C or HIV infection chose to describe their resulting

life-threatening illness and need for treatment to those around them as being "cancer" rather than hepatitis or HIV, shows that the isolation in which they had to bear their illness added a dimension beyond even cancer. Add to that the fact that so many clinicians advised them to tell no one. In effect, medical advice to live a lie, or if that's too strong, at least to limit the social network that might otherwise be there to support those who are suffering.

This shows that the stigma of having one or more of these blood-borne infections was not just something the sufferers alone recognised, their doctors did too.

Add the sad fact that the evidence suggests that there still remain pockets of ignorance and prejudice amongst, of all people, NHS staff. Add to that the worry. "Can I pass it on? Am I infecting those dear to me? Have I already done so? Dare I risk becoming a patient?" Then add the effects, the direct effects of the viruses on mind personality, and the effects of treatment, and if on personality, on relationships. All these factors make it clear that there was a need for there to have been

effective, knowledgeable, expert psychological support services on offer.

The evidence thus far has underlined that those who received infected blood and their families have suffered in all the ways I've highlighted and many, probably most, have suffered all the more because they had no such support.

Now, I'm delighted to acknowledge the very significant advances that there have been in the treatments for hepatitis, particularly hepatitis C, and HIV infection, and we heard today in thalassaemia and sickle cell and it's anticipated that genetic advances may help further. But what we have also heard this week, however, has told us that though hepatitis C itself can be cured, chronic hepatitis B cannot yet be, nor can HIV.

Anyone with either of those conditions must go on taking tablets for the rest of their lives. They may fear what the future brings. Their trust in doctors may be shaky because of the source of their infections.

We have heard that the effects of past infection and past treatment don't simply

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disappear. A damaged liver does not cease being damaged overnight because the virus that caused it has cleared. Personality and mental function may be permanently affected and we have heard that people are still scared of the way others will react to knowing that they have the disease. Hence the large take-up of the services of the intermediaries from whom we heard, and some find it difficult to access the medical services they need for other conditions because they have experienced stigma amongst NHS staff in the past.

Now, every day this week, as I've heard it, we have heard the same message: that support is needed, not just from those to whom the intermediaries gave voice, not -- we haven't heard it just from the psychosocial experts but we've heard it also from leading experts in hepatitis and leading experts in HIV, and today we've heard that psychological support remains at best patchy in some parts of the country.

So it's for those reasons that I would like to draw the attention publicly now of NHS England and hospital trusts and boards throughout the country to the fact that the need

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for specialist treatment by professionals who have a special understanding of infected blood and blood products has not gone away, now that there is greater success in treatment of the underlying conditions, that there is a need to ensure that the standards of follow-up of those who have cleared hepatitis C but have been left with a compromised liver are maintained in accordance with what the experts have set out this week, that the support of not only those infected, but their families, need special attention, and that those who have lost a partner, son, daughter, brother, sister, mother, father, grandparent or close friend must not be ignored.

I should add that I mentioned NHS England not because I'm being parochial but because, as you've just heard, both Northern Ireland and Wales have told us that they have started to answer this call by providing services bespoke to those who have been infected by blood and blood products. If they have opened the door to treatment and support, I would hope -- indeed expect -- to see England and Scotland fully follow suit.

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Though I have had no detailed dissection of any figures as yet, the evidence thus far suggests that the outlay of public funds would not be great, but also that expenditure on support and screening will save money in the long run because it will help improve and maintain health.

The evidence this week from undoubted experts of the highest calibre has demonstrated that the health of the mind affects the health of the body and the health of the body affects the health of the mind.

I hope to be able to acknowledge in the final report that proper support and follow-up will by then be in place across the UK. So much for reflection.

Looking forward. What comes next? In June and July this year we shall start hearing about the knowledge of risk, with particular reference to the Haemophilia Centres and the clinicians who practised in those centres.

Precise details will follow in due course. This is exactly as I'd anticipated at the start -- or the end, I should say -- of our hearings last October as I've just read out to

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you at the start of my reflection. We are on course as we had planned to be, and I hope you've seen from this week that it fits together to give us a proper basis for approaching what we need to do in June and July starting then.

For those of you who wish to come back and hear that, I look forward to seeing you again. Otherwise, can I just say that I wish you a very safe journey home. Thank you.

[Applause]

(4.05 pm)

(Adjourned until a date to be confirmed in June)