

<p style="text-align: right;">1</p> <p style="text-align: center;">Friday, 28th February 2020</p> <p>1</p> <p>2 (10.30 am)</p> <p>3 SIR BRIAN LANGSTAFF: Today, the last day of this</p> <p>4 week of largely expert testimony, we have</p> <p>5 another first for those of us in the Inquiry</p> <p>6 from abroad, we have Professor Rockstroh joining</p> <p>7 us from Germany.</p> <p>8 Professor Rockstroh, can you hear me?</p> <p>9 PROFESSOR ROCKSTROH: Yes, I can hear you very well.</p> <p>10 SIR BRIAN LANGSTAFF: Thank you.</p> <p>11 What we're going to do is start off by</p> <p>12 swearing in the other experts on the panel and</p> <p>13 then Mary, my clerk, will swear you in, take an</p> <p>14 affirmation from you, and then you'll be asked</p> <p>15 questions by counsel to the Inquiry.</p> <p>16 Thank you very much for joining us and</p> <p>17 making the time. We understand you have an</p> <p>18 hour, and I'm delighted to have been able to</p> <p>19 take advantage of you for that period of time at</p> <p>20 least. So thank you very much in anticipation.</p> <p>21 May the experts be sworn.</p> <p>22 MALIKA SEKHAR (affirmed)</p> <p>23 PROFESSOR DAVID EDGAR (affirmed)</p> <p>24 DR SARA MARSHAL (affirmed)</p> <p>25 DR RICHARD GOODING (sworn)</p>	<p style="text-align: right;">2</p> <p>1 DR KATE RYAN (affirmed)</p> <p>2 DR OLIVER TUNSTALL (affirmed)</p> <p>3 PROFESSOR JÜRGEN ROCKSTROH (affirmed)</p> <p>4 SIR BRIAN LANGSTAFF: Thank you very much.</p> <p>5 MS RICHARDS: Sir, before I ask the experts to</p> <p>6 introduce themselves and say a little bit</p> <p>7 themselves, I wanted to say a couple of words</p> <p>8 about the nature of the evidence we'll hear this</p> <p>9 morning and the kind of material we won't be</p> <p>10 looking at this morning.</p> <p>11 So the evidence will be following a very</p> <p>12 similar format to the evidence we've heard over</p> <p>13 the last four days, but with a slightly</p> <p>14 different focus. Whereas the focus of the last</p> <p>15 four days has been looking at impact in medical</p> <p>16 and psychosocial terms of the infections, today</p> <p>17 we're considering some of the underlying</p> <p>18 disorders or conditions which gave rise to the</p> <p>19 receipt or administration of treatment, whether</p> <p>20 by way of blood products or blood for those</p> <p>21 conditions.</p> <p>22 And as a result, the report that we have</p> <p>23 falls essentially into three parts, and our</p> <p>24 different members of the panel are likely to be</p> <p>25 dealing with different parts. So the first part</p>
<p style="text-align: right;">3</p> <p>1 looks at bleeding disorders, treated, as we</p> <p>2 know, with blood products, particularly factor</p> <p>3 concentrates.</p> <p>4 The second part of the report deals with</p> <p>5 certain inherited disorders of haemoglobin for</p> <p>6 which regular blood transfusion was a mainstay</p> <p>7 of treatment. And then the third part of the</p> <p>8 report looks at primary immunodeficiency</p> <p>9 disorders for which immunoglobulin replacement</p> <p>10 therapy was a mainstay of treatment, and so</p> <p>11 that's why there are a number of different</p> <p>12 focuses of the evidence today.</p> <p>13 In common with the approach taken to experts</p> <p>14 earlier in the week, we will not be asking</p> <p>15 questions about the correctness or otherwise of</p> <p>16 treatment decisions that may have been taken in</p> <p>17 relation to any of those disorders.</p> <p>18 So whilst the reports do have, and this</p> <p>19 report does have, a section looking at treatment</p> <p>20 for bleeding disorders in particular pre-1970</p> <p>21 and post-1970, I'm going to be asking very</p> <p>22 little about that, and I've explained that to</p> <p>23 colleagues behind. The reason for that is</p> <p>24 threefold: firstly, as the panel members have</p> <p>25 made clear to the Inquiry, they were not, in</p>	<p style="text-align: right;">4</p> <p>1 relation to bleeding disorders, clinicians</p> <p>2 practising in the 1970s and 1980s, so they don't</p> <p>3 have direct firsthand knowledge to draw on in</p> <p>4 that respect.</p> <p>5 Secondly, as a result, when they've sought</p> <p>6 to give us an overview of the picture in</p> <p>7 relation to the historic period, they have quite</p> <p>8 properly drawn on publicly available sources,</p> <p>9 which has inevitable limitations because</p> <p>10 the Inquiry has available to it far greater</p> <p>11 amounts of contemporaneous material, and we</p> <p>12 couldn't possibly ask clinicians to take time</p> <p>13 out of their full time clinical practice to look</p> <p>14 through the thousands and thousands of documents</p> <p>15 that we have relating to decisions in the 1970s</p> <p>16 and 1980s. And the third reason is that</p> <p>17 ultimately, of course, these are the questions</p> <p>18 of fact that go to the heart of issues at the</p> <p>19 Inquiry that are for you, sir, to determine.</p> <p>20 That's a long way of explaining that the</p> <p>21 focus of my questions today, as with the</p> <p>22 questions earlier this week, will be on what is</p> <p>23 currently known and understood about the</p> <p>24 relevant disorders.</p> <p>25 So after that introduction, can I ask each</p>

<p style="text-align: right;">5</p> <p>1 member of the panel to just introduce themselves 2 and say a couple of sentences about their area 3 of expertise. 4 I'll start with you, please. 5 DR SEKCHAR: I'm a consultant haematologist at the 6 Royal Free Hospital and University College 7 Hospital, and this has been since 2011. 8 I qualified in 1982 and came to England in '87. 9 I had then worked for a bit as a registrar 10 trainee and then became a consultant in '95. 11 My main responsibilities are, at the present 12 time, to look after some patients -- some 13 categories of patients with certain types of 14 blood cancers, and to be the lead for the Blood 15 Transfusion Service at the two hospitals I work 16 in. 17 MS RICHARDS: Professor? 18 PROFESSOR EDGAR: My name is David Edgar, I'm 19 a consultant immunologist. I qualified in 20 medicine in 1995 and I was appointed consultant 21 in Belfast in -- sorry, in 1985 and I was 22 appointed consultant in Belfast in 1996. 23 Over the last year I've been working in 24 Saint James's Hospital in Dublin, and my main 25 interest relevant to this Inquiry is looking</p>	<p style="text-align: right;">6</p> <p>1 after patients with primary immunodeficiencies 2 who would receive immunoglobulin replacement, 3 but I also run a laboratory service and also an 4 allergy service. 5 DR MARSHALL: My name is Sara Marshall and I'm 6 a consultant clinical immunologist and for the 7 last 35 years I've been involved in the care of 8 patients with immune problems, both immune 9 deficiencies and autoimmune diseases. I've also 10 had a research career and I currently work for 11 a research charity called the Wellcome Trust, 12 where I am head of clinical research. 13 DR GOODING: My name is Richard Gooding. I'm 14 a consultant haematologist working in Leicester, 15 and I qualified in 2003 and became a consultant 16 in 2012. I'm currently the Haemophilia Centre 17 director of the Comprehensive Care Centre in 18 Leicester, and my special area -- my areas of 19 special interest are haemophilia and I manage 20 both adult and paediatric patients with bleeding 21 disorders, and I also manage patients with 22 thrombotic disorders and manage 23 anti-coagulation. 24 DR RYAN: Good morning, my name is Kate Ryan. I'm 25 presently a consultant haematologist in</p>
<p style="text-align: right;">7</p> <p>1 Manchester. I qualified in 1981 and trained in 2 London before becoming a consultant in 3 West London in 1994, moved to Manchester 4 in 2011. I have been looking -- my specialist 5 interest is inherited haemoglobinopathy, so 6 sickle cell, thalassaemia and other rare 7 inherited anaemias, and I have about 30 years' 8 experience of managing these conditions. 9 DR TUNSTALL: My name is Oliver Tunstall. I'm 10 a consultant paediatric haematologist in Bristol 11 Royal Hospital for Children. I qualified in '96 12 and have been a consultant since 2010. I run 13 the Paediatric Haemophilia Service and the 14 South-west Paediatric Haemophilia Network. As 15 well as managing children's bleeding disorders, 16 I also manage other blood disorders in children. 17 MS RICHARDS: Professor Rockstroh. 18 PROFESSOR ROCKSTROH: Yes. So I was qualified in 19 1989 at the -- and I started working at the 20 department of medicine, University Hospital in 21 Bonn, where I did my internal medicine and 22 infectious diseases training and became 23 a consultant of infectious diseases in 1998. 24 The story is that in Bonn we have the very large 25 cohort of haemophiliacs, 420, so it's the</p>	<p style="text-align: right;">8</p> <p>1 largest existing cohort with HIV infection, was 2 treated in our HIV clinic, and that's where 3 I spent my clinical work -- did my clinical 4 work, and also my research, which has been 5 mostly around HIV and hepatitis co-infection, in 6 the last 30 years. 7 MS RICHARDS: Thank you. 8 Professor Rockstroh, as we only have you for 9 a limited period of time I'm going to start with 10 questions I think you're probably best able to 11 help us with, which is looking at the 12 implications of HIV and hepatitis co-infection, 13 in -- specifically for those who have a bleeding 14 disorder. 15 Can I ask you, first, to concentrate on the 16 position of individuals with a bleeding disorder 17 who are infected with HIV. That's my first set 18 of questions. 19 PROFESSOR ROCKSTROH: Yes. 20 MS RICHARDS: Can I just ask, first of all, are 21 there any studies or research that you're aware 22 of that focus on HIV in what I might call the 23 wider infected blood community? So looking at 24 those who were infected as a result of treatment 25 for bleeding disorders, but also partners who</p>

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1 may have become infected and the broader family
 2 position. Do you know of any research or
 3 studies in that field?
 4 **PROFESSOR ROCKSTROH:** Yes, so we obviously analyse
 5 our own cohort of infected haemophiliacs, so
 6 then there's a limitation that it's mostly
 7 haemophiliacs. We have some von Willebrand's
 8 but not -- but at least numerically that's much
 9 lower, and we also looked at their partners.
 10 We had -- 10% of the female partners got HIV
 11 infected, and we have a paper published on that.
 12 The overall course of HIV in haemophiliacs or
 13 other bleeding disorders is not too much
 14 different from other patients who acquire HIV.
 15 So, in my analysis -- because that's what I did
 16 my research on -- it looked as if the outcome
 17 was maybe a little bit more favourable in
 18 haemophiliacs, mostly based on the fact that
 19 they do not develop Kaposi's sarcoma, which was
 20 very prominent in gay men, and also if it became
 21 pulmonary or, you know, manifestations in the
 22 (inaudible) bleeding events and chemotherapy was
 23 difficult with advanced immunodeficiency KS to
 24 varied terms, and that may have contributed to
 25 some of those people dying from KS. In the

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1 episodes. But I have to say that in the context
 2 of hepatitis C, you can also develop
 3 thrombocytopenia which is a sign of advanced
 4 liver (unclear) cirrhosis. If you HIV and
 5 hepatitis C and you had, sort of
 6 thrombocytopenia which was enhanced in the
 7 setting of cirrhosis that could have actually
 8 had an impact and indeed was more likely to lead
 9 to bleeding events. Obviously that also plays
 10 a role in the setting of advanced liver disease
 11 when you have varices and can die from
 12 (inaudible).
 13 **MS RICHARDS:** I'll come on to hepatitis C for a
 14 moment but just sticking with HIV and bleeding
 15 disorders, treatment for HIV have there been any
 16 particular adverse impacts from HIV treatment?
 17 Obviously we know there are lots of adverse
 18 impacts from the treatment itself but
 19 specifically on a bleeding disorder. You've
 20 identified in the reports some reports of
 21 increased bleeding episodes under commonly used
 22 first generation protease inhibitors, I think.
 23 **PROFESSOR ROCKSTROH:** Yes. So there was in
 24 particular a German group in Munster which
 25 reported an increased bleeding frequency in

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1 setting of IV drug users, you obviously have
 2 a high rate of suicide and overdosing so that
 3 had a little impact on their overall survival,
 4 but in general terms speaking, the overall
 5 average time in untreated HIV was around
 6 10 years, and after an AIDS defining event was
 7 2 years. So -- and that honestly all changed
 8 with the advent of antiviral therapy, but really
 9 the overall figures are very comparable to other
 10 groups.
 11 **MS RICHARDS:** I think you've identified in the
 12 report, because you contribute also to the
 13 hepatitis and HIV reports, you've identified
 14 I think one particular impact that HIV may have
 15 on a person with a bleeding disorder which is
 16 that it can cause thrombocytopenia which may
 17 increase the bleeding risks; is that right?
 18 **PROFESSOR ROCKSTROH:** Yes, in consideration of the
 19 increased bleeding risks overall in the setting
 20 of a bleeding disorder, I listed that because
 21 it's the only HIV-associated manifestation which
 22 could have an impact, I think it's fair to say,
 23 though that mostly patients with low clot, which
 24 is a common finding in untreated HIV infection,
 25 didn't really lead to a lot of bleeding

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1 haemophiliacs receiving first generation
 2 protease inhibitors for HIV therapy. This was
 3 not really reproduced in our cohort but I have
 4 to say our haemophilia treatments had different
 5 substitution policy which was always leaning
 6 towards the preventive substitution; daily
 7 administration of factor, units to prevent any
 8 kind of bleeding episode which may have covered
 9 this increased risk. So if you are in a centre
 10 with a strategy which was less frequent in
 11 administration of blood factors, then that might
 12 have been true, and we would have covered it in
 13 our cohorts. There are reports in literature
 14 which do suggest there may have been a higher
 15 bleeding episode risk under HIV protease
 16 inhibitors.
 17 **MS RICHARDS:** Looking at it the other way round, you
 18 touched on this already, but the impact of
 19 bleeding disorder on the progression or severity
 20 of HIV or treatment for HIV, you've identified
 21 in your report obviously what you describe as
 22 profound and multi-factorial impacts of HIV on
 23 this cohort but from a clinical perspective (and
 24 leaving aside Kaposi's sarcoma which you've
 25 addressed separately), as I understand your

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1 report, the clinical course of HIV or AIDS is
 2 not materially affected usually by the cause of
 3 transmission, the transmission risk group that
 4 the individual fell within.
 5 **PROFESSOR ROCKSTROH:** Correct. I mean, obviously it
 6 is -- all the differences you see between the
 7 different key populations really comes from
 8 lifestyle, right. In the drug users you have
 9 all these additional aspects. You consider the
 10 haemophiliacs were, you know, more likely to be
 11 into therapy, and come for visits and so forth.
 12 So that's maybe why they have just a little bit
 13 of a better outcome compared to IV drug users.
 14 But otherwise I think there is really no
 15 difference. It was the same natural course.
 16 **MS RICHARDS:** You've identified in your report that
 17 one factor that seems to make a significant
 18 influence on survival rates was age at time of
 19 HIV seroconversion; is that right? Is it
 20 understood why --
 21 **PROFESSOR ROCKSTROH:** That's correct.
 22 Well, I think we have to appreciate that
 23 with age you also have changes in your immune
 24 system, so in general you would think that
 25 someone who is aging that probably a loss of C4

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1 **MS RICHARDS:** Then in relation to hepatitis C, can
 2 I ask similar questions. What impact does
 3 hepatitis C have on a person with a bleeding
 4 disorder or for treatment for their bleeding
 5 disorder?
 6 **PROFESSOR ROCKSTROH:** Yes, I think it doesn't really
 7 have an impact on the treatment of the bleeding
 8 disorder, but obviously the liver disease can
 9 eventually move on to liver probiosis, cirrhosis
 10 and bleeding complications like resal(?)
 11 bleeding and that can obviously be enhanced in
 12 the setting of a bleeding disorder.
 13 **MS RICHARDS:** For hepatitis C, are there any
 14 particular issues in relation to treatment for
 15 hepatitis C? We've heard a lot about the side
 16 effects and adverse events associated with the
 17 interferon in treatments, but were there
 18 specific problems for those with bleeding
 19 disorder either in terms of impact, different
 20 side effects, or resistance to treatment?
 21 **PROFESSOR ROCKSTROH:** I think, in general, because
 22 most of the haemophiliacs had a genotype 1A
 23 infection, that seemed to respond less
 24 favourably than some of the genotype infections.
 25 So I think the prevalence of more advanced liver

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1 count would be more meaningful because per se in
 2 the setting of age-associated immunodeficiency
 3 you would be more likely to be prone for
 4 infections. So bacterial infections may be more
 5 prominent and so forth. I would say, yes, age
 6 is a big player in that setting.
 7 **MS RICHARDS:** Were there any treatments for
 8 AIDS-defining conditions that wouldn't have been
 9 available to those with bleeding disorders?
 10 **PROFESSOR ROCKSTROH:** Let me think. So the majority
 11 of patients I saw first developed usually fungal
 12 disease, so they had oral thrush and then
 13 oesophageal candidiasis, and that could be
 14 treated equally well. There's always the
 15 limitation that patients with haemophilia or
 16 other bleeding disorders had hepatitis C, so the
 17 risk of hepatitis toxicity is clearly enhanced
 18 in this patient population. So that would be
 19 one limitation. Obviously in this setting of
 20 liver cirrhosis, if you treat tuberculosis or
 21 other things where you bleed a lot, there are
 22 toxic drugs that could have had an impact on the
 23 dosage or the duration of your therapies because
 24 of side effects, but in general you can use the
 25 same drugs.

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1 disease was higher, the unfavourable genotype,
 2 and so overall if you look at the treatment
 3 outcome of interferon-based regimens in
 4 haemophiliacs always intended to be somewhat
 5 lower. Now, unfortunately that has all
 6 disappeared in the DAA, where everyone is
 7 responding so well, but clearly treatment for
 8 haemophiliacs in the early days was relatively
 9 challenging with regard to the outcome, which
 10 always tended to be a little poorer, and so
 11 a lot of haemophiliacs were not willing to
 12 undergo this intervention because of the low
 13 promise of cure following this intervention.
 14 **MS RICHARDS:** Are there any studies or research that
 15 you can direct us to looking at life expectancy
 16 for those with bleeding disorders infected with
 17 HIV, hepatitis C, or both?
 18 **PROFESSOR ROCKSTROH:** Yes. Well --
 19 **MS RICHARDS:** I'm not necessarily asking for a list
 20 now but if you can tell us what you know and we
 21 may ask you to supply more details in writing.
 22 **PROFESSOR ROCKSTROH:** Yes, so obviously the -- so
 23 the life expectancy is affected by all of these
 24 concomitant diseases, so even in the setting of
 25 having just hepatitis C you still have a higher

<p style="text-align: right;">17</p> <p>1 risk of developing liver cirrhosis and hepatic 2 carcinoma, and dying from these complications, 3 so that's still much higher, so that impacts 4 obviously your overall survival. 5 In the setting of HIV, you obviously have 6 a diminished survival with regards to the old 7 days, where we didn't have any anti-viral 8 regimens. And then I think what is particularly 9 important in the context of HIV and hepatitis 10 co-infection, because obviously most of the 11 patients had hepatitis C, so if you had HIV 12 you're likely to have -- having hepatitis C, the 13 risk was very, very high, then you had an 14 even -- much more increased risk of dying from 15 liver disease. And that was particularly true 16 if you belonged to those people who started to 17 develop more (inaudible) immunodeficiency. So 18 the more CD4 count you lost, the higher your 19 risk of dying from liver disease. And that has 20 been also the reason why there were 21 particularly -- guidance in the -- European 22 treatment guidelines for people with 23 co-infection to start HIV therapy earlier to 24 prevent the CD4 count loss which then triggered 25 the faster fibrosis progression in these</p>	<p style="text-align: right;">18</p> <p>1 patients. 2 Then the patients who had, beyond HIV and 3 hepatitis C, also additional hepatitis B 4 infection, was also associated with a more 5 unfavourable outcome. Then there were patients 6 with hepatitis B, C and D. And just to 7 underline the significance of these viral 8 interactions, of all the haemophiliacs we had, 9 every patient with hepatitis B, C, and D and HIV 10 died prior to the advent of highly successful 11 antiviral therapy, because the outcome of liver 12 disease was the worst, and the patients all died 13 prior to the onset of having these regimens 14 available. 15 So that's really the worst outcome 16 altogether but clearly liver disease has been 17 the main issue in the station(?) population for 18 all the different viral infections. 19 MS RICHARDS: And there is faster liver disease 20 progression, faster progression to fibrosis and 21 beyond, in co-infected patients? 22 PROFESSOR ROCKSTROH: Yeah, and so -- and we were 23 one of the first groups to examine that because 24 we saw patients turn yellow, basically, really, 25 in clinic. At first I thought it might be</p>
<p style="text-align: right;">19</p> <p>1 related to the anti-retroviral drugs we were 2 using, different elimination and potential 3 accumulation of toxicities in patients who were 4 cirrhotic, but then it really turned out that in 5 the setting of low CD4 counts, patients had an 6 accelerated fibrosis (inaudible) compared to 7 stable CD4 counts, stable-wise haemophiliacs 8 with those who had (inaudible) immunodeficiency 9 and really saw that that was the group where we 10 saw a lot of people dying from liver disease. 11 So we could clearly establish that. 12 I think one of the interesting questions 13 was: is this reversible if you start giving HIV 14 therapy and have an increase in CD4 count? And 15 there are big cohorts from the United States 16 looking at that and showing that even with the 17 setting up -- giving antiviral therapy, you 18 probably still have a somewhat faster fibrosis 19 progression. So unfortunately HIV does take an 20 impact on the negative side there. 21 MS RICHARDS: Then can I ask about a different way 22 in which there may have been a burden or impact 23 for those with bleeding disorders infected 24 with HIV and/or hepatitis C, and that's the 25 burden of treatment. These are individuals who</p>	<p style="text-align: right;">20</p> <p>1 will already be having to, particularly if they 2 have a severe bleeding disorder, have 3 a substantial amount of treatment. Add to that 4 the burden of treatment for HIV, and we heard 5 a lot of evidence yesterday about how 6 problematic the HIV treatments were in the early 7 decade, and then add to that the burden of the 8 interferon era treatment. Is that something 9 that you observed in your clinical practice? 10 PROFESSOR ROCKSTROH: Yeah, absolutely. I think 11 there are even some things to add because, first 12 of all, not only do you have, you know, all 13 these issues with the various drug treatments 14 for different diseases, but in the setting of 15 co-infection we also recommended longer 16 interferon durations, which were very burdensome 17 for the patients to tolerate, and unfortunately 18 because the infections were acquired so early -- 19 which means that a lot of the patients had to 20 start early HIV drugs, with a lot of side 21 effects. 22 So if you look at patients today, when they 23 start anti-retroviral treatment, it's really 24 different because the amount of patients 25 discontinuing therapy because of side effects is</p>

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

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1 obviously you don't want to let HIV replicate.
 2 So HIV control is your first absolute must. And
 3 then you have to see with which drugs is that
 4 possible, and does that allow co-administration
 5 with some of the other drugs, or is this going
 6 to lead to enhanced toxicity, and do you have
 7 to, I don't know, give EPO(?) or transfusions to
 8 compensate certain enhanced toxicities? So
 9 there were clearly special aspects around
 10 drug-drug combinations.
 11 I wouldn't say that there was any real
 12 contraindication in general, other than that
 13 obviously the setting of cirrhosis you also have
 14 contraindications for -- so you can treat with
 15 somebody with decompensated cirrhosis, for
 16 example, in the interferon, and you can't treat
 17 someone with decompensated cirrhosis with most
 18 of the DAAs because they're not licensed for
 19 more advanced child stages. So there are some
 20 limitations reflecting on liver disease stage
 21 and drug interactions.
 22 **MS RICHARDS:** Professor Rockstroh, thank you.
 23 I'm going turn to some more general
 24 questions about bleeding disorders, which will
 25 be directed at the panel sitting here. But

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1 **MS RICHARDS:** And presumably one might add to that
 2 somewhat complex picture, not just the treatment
 3 for the bleeding disorder, the hepatitis,
 4 the HIV, but the potential regimes of treatment
 5 that an individual might undergo for -- to deal
 6 with the side effects of treatment, the
 7 AIDS-defining conditions that might have been
 8 developed --
 9 **PROFESSOR ROCKSTROH:** Yeah.
 10 **MS RICHARDS:** -- the psychological and mental
 11 effects of everything that individuals were
 12 undergoing. So there may have been
 13 a multiplicity of treatments.
 14 **PROFESSOR ROCKSTROH:** Absolutely.
 15 **MS RICHARDS:** Do you know whether there were
 16 specific contraindications for different
 17 treatments or particular problems experienced by
 18 this cohort in terms of receiving treatment for
 19 the wide range of side effects and other
 20 consequences they might have been experiencing?
 21 It's a long way of putting a question.
 22 **PROFESSOR ROCKSTROH:** Well -- yes, well, there were
 23 some contraindications coming from drug-related
 24 interactions, and so in the end you had to look
 25 at every patient and see what was -- because

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1 please do, in the time you have with us, I think
 2 we've got you for another 25 minutes or so on
 3 the line before you have other clinical
 4 commitments, please do join in, contribute, add
 5 to anything that's being said by your
 6 colleagues.
 7 **DR SEKHAR:** Could I just make a couple of comments?
 8 **MS RICHARDS:** Yes, of course.
 9 **DR SEKHAR:** One is about platelets. So
 10 thrombocytopenia was a problem, and is
 11 a problem, in this group of patients. One of
 12 the things we learned through the early nineties
 13 was treating the HIV can improve the
 14 thrombocytopenia, and so we became more and more
 15 confident about treating thrombocytopenia in the
 16 HIV patient cohort.
 17 The second thing is that in the last
 18 10 years or so, treating thrombocytopenia has
 19 become more easy and this is especially with
 20 relevance to the hepatitis C group of patients
 21 and there are new drugs introduced and clinical
 22 trials done. So again, treating
 23 thrombocytopenia has become easy. It still is
 24 a problem but it's now possible to treat them
 25 such that it doesn't interfere with other

<p style="text-align: right;">25</p> <p>1 things.</p> <p>2 MS RICHARDS: Thank you.</p> <p>3 DR SEK HAR: The second point is about biopsies in</p> <p>4 patients with bleeding disorders who might have,</p> <p>5 say, AIDS-related lymph node enlargements. It</p> <p>6 was not easy to do that because they were having</p> <p>7 a bleeding problem but it was also very</p> <p>8 difficult in the initial stages to have proper</p> <p>9 correct types of diagnosis because people didn't</p> <p>10 know, histopathologists didn't know, how to</p> <p>11 interpret what they were seeing under the</p> <p>12 microscope. So it took a while before they</p> <p>13 could distinguish it from cancers and just</p> <p>14 HIV-related changes.</p> <p>15 MS RICHARDS: Thank you.</p> <p>16 So I'm going to turn to the first part of</p> <p>17 the report, and ask questions about what's</p> <p>18 currently known about some of the key bleeding</p> <p>19 disorders, and what the current treatment</p> <p>20 regimes are for them.</p> <p>21 I'm going start with haemophilia A, and ask</p> <p>22 a member of the panel (perhaps Dr Gooding and</p> <p>23 Dr Tunstall) to tell us first of all, what is</p> <p>24 haemophilia A? I'm conscious that many people</p> <p>25 here will have a much greater knowledge about</p>	<p style="text-align: right;">26</p> <p>1 any of us about that, but part of our purpose in</p> <p>2 asking these questions is wider public</p> <p>3 education.</p> <p>4 DR GOODING: Haemophilia A is a bleeding disorder</p> <p>5 obviously, characterised by reduction of one of</p> <p>6 the clotting factors, Factor VIII. It ranges in</p> <p>7 severity from a very mild condition to</p> <p>8 potentially very severe and it's characterised</p> <p>9 by bleeding into, typically, muscles and joints.</p> <p>10 The bleeding severity tends to correlate quite</p> <p>11 well with the levels of Factor VIII that are</p> <p>12 detectable in the bloodstream. So a very</p> <p>13 significant reduction, so typically between 1</p> <p>14 and 3 per cent is characterised by a severe</p> <p>15 bleeding tendency.</p> <p>16 We can see essentially what we call</p> <p>17 spontaneous bleeding but it's essentially driven</p> <p>18 by normal activities. It's not truly</p> <p>19 spontaneous. We don't see it in very young</p> <p>20 infants until they start walking, usually. It's</p> <p>21 that sort of level of very mild trauma within,</p> <p>22 say, joints and muscles that can lead to this</p> <p>23 sort of what we call spontaneous bleeding. Then</p> <p>24 that can lead to, well, obviously the acute</p> <p>25 problem, so that sort of pain, discomfort,</p>
<p style="text-align: right;">27</p> <p>1 reduced mobility, and that sort of thing and</p> <p>2 then much longer term problems with joint</p> <p>3 damage.</p> <p>4 MS RICHARDS: Haemophilia A mostly affects males.</p> <p>5 I'm going to come on to the questions</p> <p>6 specifically about how it affects females later.</p> <p>7 (Witness nodded)</p> <p>8 Do you know approximately how many people</p> <p>9 with haemophilia A there are currently in the</p> <p>10 United Kingdom?</p> <p>11 DR GOODING: I haven't got that statistic with me,</p> <p>12 actually. It's part of the UKHCDO statistics</p> <p>13 but I don't have that with me off the top of my</p> <p>14 head.</p> <p>15 MS RICHARDS: Don't worry. We can extract that from</p> <p>16 the national reports.</p> <p>17 DR TUNSTALL: Yes, it's in the thousands.</p> <p>18 DR GOODING: Yes.</p> <p>19 MS RICHARDS: In terms of what causes haemophilia A</p> <p>20 or how people may come to have haemophilia A,</p> <p>21 it's an inherited condition, but not for</p> <p>22 everybody. There are some for whom it occurs</p> <p>23 spontaneously through genetic mutation with no</p> <p>24 family history; is that right?</p> <p>25 DR GOODING: Yes. I suppose if you're looking at it</p>	<p style="text-align: right;">28</p> <p>1 in terms of inherited and not inherited, there's</p> <p>2 the more common inherited form in which there's</p> <p>3 a problem with the X chromosome and that can</p> <p>4 either be inherited, you know, as in predictably</p> <p>5 through a family, so there's a known diagnosis,</p> <p>6 but it can occur with a spontaneous mutation as</p> <p>7 well and that's about 50 per cent of cases that</p> <p>8 are seen in that way. So that's all inherited.</p> <p>9 There is an acquired form of haemophilia as</p> <p>10 well which is an autoimmune disorder which is</p> <p>11 typically seen in older adults. That's an</p> <p>12 autoimmune condition, so that's very different.</p> <p>13 So in that individual, they will have had normal</p> <p>14 levels of Factor VIII and then an antibody will</p> <p>15 have been produced which will reduce the</p> <p>16 effectiveness or the levels of Factor VIII. So</p> <p>17 those are the sort of differences there.</p> <p>18 DR TUNSTALL: Sorry, can I just -- we do use the</p> <p>19 term "inherited" in a slightly confusing way,</p> <p>20 I think, in that "inherited" is often used as</p> <p>21 synonymous with congenital with birth or genetic</p> <p>22 in that sense. So even cases where there</p> <p>23 haven't been recognised cases of haemophilia in</p> <p>24 the family, we would still consider it an</p> <p>25 inherited bleeding disorder, because it's --</p>

29

1 **MS RICHARDS:** Because it's not acquired in the way
 2 that's just been described?
 3 **DR TUNSTALL:** As opposed to acquired, yes.
 4 **MS RICHARDS:** In terms of diagnosis with haemophilia
 5 A, as I understand it from the report, there may
 6 be what you call targeted testing of a baby
 7 because there's a known history of haemophilia A
 8 in the family, or there may be children who
 9 present with symptoms, bruising, bleeding
 10 without a family history; is that right?
 11 **DR TUNSTALL:** So that's right. So if we're aware of
 12 haemophilia in the family and we are aware that
 13 a pregnant woman is known to carry -- have one
 14 copy of the affected Factor VIII gene, then they
 15 typically should be referred to see
 16 a haematologist during the pregnancy and then
 17 plans can be made.
 18 There are various choices about when testing
 19 can be done. So there's the option of antenatal
 20 testing, antenatal genetic testing of the
 21 foetus, or plans can be put in place to test
 22 a newborn baby immediately which is usually done
 23 on cord blood.
 24 Then there are the cases that come to light
 25 for other reasons, typically for severe

31

1 In haemophilia A, one would expect a very
 2 prolonged APTT, certainly in severe haemophilia
 3 A, than an extremely prolonged APTT and then
 4 that would lead hopefully in the clinical
 5 context to more specialised testing of the
 6 Factor VIII activity within the blood.
 7 **MS RICHARDS:** Then we have as we've heard -- and
 8 indeed we've heard from a lot of the evidence
 9 we've heard from individuals -- the
 10 classification of haemophilia A into severe to
 11 moderate and mild. I think you've touched on
 12 the levels that would identify severe
 13 haemophilia. Could you just talk us through the
 14 different levels of Factor VIII that would lead
 15 to someone being classed as mild, moderate, and
 16 severe?
 17 **DR GOODING:** Typically, the classification would be
 18 that severe patients would have less than
 19 1 per cent Factor VIII levels, moderate patients
 20 would be between 1 and 5, and then mild would be
 21 5 up to perhaps 30 or to the lower limit of
 22 normal. So that's the classification.
 23 Although, there is -- I mean, as with anything
 24 in life, you know, it's a description of a more
 25 complex sort of system, really. So there are

30

1 haemophilia that's very early on in life, that
 2 they're noticed to have (bruising or bleeding
 3 within the first year or two of life) and then
 4 typical investigations, the basic screening
 5 clotting screens are usually grossly abnormal,
 6 and hopefully somebody puts two and two together
 7 and the more specialised testing is done and
 8 they're referred to a specialist team.
 9 **MS RICHARDS:** In terms of that specialised testing,
 10 you've identified two sets of tests, something
 11 called APTT and then factor assays. I wondered
 12 if you could briefly explain what those are for
 13 us.
 14 **DR TUNSTALL:** They're tests that are done very
 15 commonly in a hospital, something called
 16 a coagulation screen or a clotting screen which
 17 consists of tests where basically blood is spun
 18 into its cellular component in the plasma and
 19 the plasma (which is the liquid component of
 20 blood) is then tested with activators to see how
 21 quickly it forms a blood clot. You can use
 22 different activators and they give rise to the
 23 PT and the APTT. Those timings are, to
 24 a certain extent, predictive of levels of the
 25 soluble clotting factors such as Factor VIII.

32

1 other factors that can lead to bleeding and so
 2 there is some, whilst that's a -- there is good
 3 correlation and that's a NICE classification,
 4 then there may be people who, for one reason or
 5 another, may have a more severe phenotype and
 6 more severe sort of expression even though their
 7 levels are slightly higher, or who conversely
 8 might be seen to be relatively protected for
 9 other reasons, even though the levels of
 10 Factor VIII are low.
 11 So it's not an absolute but it's probably
 12 the best description that we've got, really.
 13 **MS RICHARDS:** I wasn't going to ask you anything
 14 historical so please tell me if you can't answer
 15 this, but are those levels ones that have been,
 16 as far as you know, fixed in clinical practice
 17 for a significant period of time or have there
 18 been a number of changes over the years?
 19 **DR GOODING:** They're pretty fixed, aren't they?
 20 **DR TUNSTALL:** I believe in the UK we often use less
 21 than 2 as severe rather than less than 1.
 22 Then there was an attempt standardise things
 23 internationally which use less than 1. There's
 24 actually a sort of growing movement as the
 25 evolution -- there are practical implications

33

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

11 **SIR BRIAN LANGSTAFF:** Before you go on, the
 12 percentage is obviously a percentage of
 13 something. It would imply 100 per cent, so
 14 1 per cent is 100th of that, but what is
 15 100 per cent? I understand that's not, as it
 16 were, the most you can get. That's normal, is
 17 it?

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

23 **SIR BRIAN LANGSTAFF:** The average or the median?

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

35

1 **DR GOODING:** It is an important point, though
 2 actually, mentioning percentage because it does
 3 sound confusing because to have 50 per cent
 4 being normal just sounds strange. But it is
 5 just the terminology that's used. So yes,
 6 100 per cent. We're not aiming -- you know,
 7 100 per cent is not haemostatically significant,
 8 necessarily. You might be aiming for
 9 50 per cent or 40 per cent and that may be okay
 10 in terms of having a response to treatment, for
 11 example. You might consider a normal range to
 12 be down to around 50 per cent, like you said.
 13 It just sounds like it doesn't make sense.

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

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

34

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

4 **SIR BRIAN LANGSTAFF:** Arising out of counsel's last
 5 question to you, has the sense of what
 6 100 per cent is or the normal (50 to 150
 7 per cent) is, has that changed over time or has
 8 that been broadly consistent in terms of
 9 international units?

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

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

36

1 be the same across the country.

2 **SIR BRIAN LANGSTAFF:** Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

16 **MS RICHARDS:** You've explained in your report that
 17 without treatment these bleeds can be painful
 18 and debilitating and sometimes fatal. I just
 19 wanted to again explore that a little more
 20 because what you've also said in your report is
 21 that typically those with severe haemophilia may
 22 suffer severe disability and early death.

23 I wondered what that suggestion might be based
 24 on in terms of any research or studies because
 25 presumably, for a number of decades, people with

40

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

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

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

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

41

1 down there; tongue bleeds could be fatal;

2 bleeding from the gut, anywhere down the gut

3 could be fatal; operative bleeding could be

4 fatal.

5 **SIR BRIAN LANGSTAFF:** Presumably the effects of

6 progressive immobility also has an effect in

7 itself in shortening life.

8 **DR TUNSTALL:** One would imagine in general, yes.

9 **DR SEKHAR:** Can I just add, in some of the reports

10 from the 1970s there are lists provided about

11 the sites of bleeding and they're usually split

12 into brain bleeding and other types of bleeding.

13 The other types include this but also soft

14 tissue; so bleeding into muscles is also

15 a problem.

16 **MS RICHARDS:** Is there any data that you're aware of

17 that would assist in understanding the frequency

18 of those types of bleeds that you've just been

19 describing (so the ones that can have a fatal

20 outcome) in those with haemophilia A who receive

21 treatment? It may be the answer is there isn't

22 any.

23 **DR TUNSTALL:** I think it's very difficult to have

24 good cross-sectional data without any treatment

25 nowadays, to be able to understand numbers, yes.

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1 on your baseline starting point. If there's no

2 Factor VIII at all, it's not likely to change

3 but if you have a degree of, you know, a sort of

4 milder sort of level of reduction, then it can

5 change.

6 We see that in female carriers as well. If

7 a woman is a carrier of haemophilia and has

8 a slightly lower Factor VIII level, which we do

9 see, then typically those sorts of levels will

10 fluctuate, a good example being in pregnancy

11 where the levels may start at, I don't know,

12 25/30, something like that, and then normalise

13 through the pregnancy and then drop back down

14 again. So there is some variability, and

15 I guess we'll touch on that later, but that

16 tends to mirror the sorts of time periods where

17 von Willebrand's levels can fluctuate as well.

18 **MS RICHARDS:** Before we talk about the different

19 treatments that are currently available for

20 haemophilia A, can I just ask you some questions

21 about how one might manage the condition without

22 treatment.

23 Now, I think both of you, your professional

24 careers in relation to haemophilia have been in

25 the recombinant era so these questions may not

42

1 **MS RICHARDS:** What we've been focusing upon there is

2 something which would be predominantly a concern

3 for those with severe haemophilia A rather than

4 mild or moderate; is that fair?

5 **DR GOODING:** Mainly, yes. I mean, obviously it is

6 possible that, like you said, postoperative

7 bleeding can happen with mild or moderate

8 haemophilia. Bleeding into the brain can happen

9 as well and into the GI tract. So it's not

10 entirely unique but it's a higher risk in --

11 **DR TUNSTALL:** It's rates of bleeding that really

12 vary between severities and it would be unusual

13 to see, as Richard describes, spontaneous

14 bleeding in those with mild haemophilia, as it's

15 termed. But bleeding still occurs and bleeding

16 can be very significant, very serious.

17 **MS RICHARDS:** And do factor levels or the severity

18 of a bleeding disorder fluctuate naturally over

19 a person's lifetime?

20 **DR TUNSTALL:** In general, no.

21 **DR GOODING:** But for more mild disease you might see

22 sort of fluctuations. So typically Factor VIII

23 levels would be higher for the first six months

24 of life and then bottom out and then maybe

25 gradually rise. So it does depend a little bit

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1 have much resonance for you, but advice about

2 managing activity, advice about bed rest, advice

3 about not undertaking certain activities, that

4 can, in principle at least, form part of

5 haemophilia care. Does it form much of a part

6 of modern haemophilia care?

7 **DR GOODING:** Probably less so, but --

8 **DR TUNSTALL:** I mean, we -- so the philosophy in

9 general, I mean certainly speaking about

10 managing children with haemophilia these days is

11 for them to lead as normal a life as is

12 possible, and we try to facilitate them living

13 a normal life. We do put certain limitations,

14 and those limitations usually are don't take up

15 rugby and don't do contact martial arts or

16 boxing. But tends to be as limited as that.

17 There can be a case if there are certain

18 activities that are particularly risky, then we

19 would have discussions about them. So, you

20 know, we have patients doing downhill mountain

21 biking and just how you manage the risk

22 associated with that, and we might have boys who

23 are playing a high level of football who are

24 seeing problems with their ankles, and you have

25 to have realistic conversations. But it's

45

1 generally a discussion about how best, how we
 2 balance risks and limit them as little as
 3 possible.
 4 We do use rest, secondary rest in management
 5 after a bleed at times -- not usually bed rest
 6 as such, but a period of relative rest or
 7 non-weight bearing to help manage a bleed.
 8 **MS RICHARDS:** Then before we look at any particular
 9 treatments, which we can do after the break,
 10 just talking about the philosophy of treatment,
 11 and again, these are questions about what you
 12 would currently do. The primary aim of
 13 treatment is to increase the levels of
 14 Factor VIII. That's why you would give
 15 treatment?
 16 **DR TUNSTALL:** The primary aim of treatment is to
 17 allow people with haemophilia to have normal
 18 lives. To do that, we want to prevent bleeds.
 19 To do that, we want to increase the level of
 20 Factor VIII and/or if they have a bleed, then
 21 the primary way of managing that bleed is to
 22 increase the amount of Factor VIII.
 23 **DR GOODING:** Just one other thing on that point,
 24 whilst that has been up until very recently the
 25 aim, there are some new treatments which

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1 **PROFESSOR ROCKSTROH:** No, I think all the aspects
 2 were covered and it sort of reflects our own
 3 experiences well and so I'm all fine with what
 4 has been said and expressed.
 5 **MS RICHARDS:** Thank you.
 6 **SIR BRIAN LANGSTAFF:** I think we have to say goodbye
 7 to you at this stage, because your time is
 8 limited, Professor.
 9 **PROFESSOR ROCKSTROH:** Yes, thank you very much.
 10 **SIR BRIAN LANGSTAFF:** Thank you, thank you,
 11 enormously. It's been a privilege for us to
 12 have had you online, and in a busy schedule. So
 13 thank you very much indeed.
 14 We'll take a break ourselves now for half an
 15 hour, to allow those who are listening to have
 16 coffee, or whatever. And we will return without
 17 you, I'm afraid, but thank you very much.
 18 [Applause]
 19 **PROFESSOR ROCKSTROH:** Thank you.
 20 (11.33 am)
 21 (A short break)
 22 (12.04 pm)
 23 **MS RICHARDS:** You set out in your report the current
 24 standard of care for a child diagnosed, first of
 25 all, with severe haemophilia. Can you tell us

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1 technically don't affect Factor VIII but still
 2 have the same effect. So it is about
 3 reducing -- normal quality of life and reducing
 4 bleeding with whatever medicines we've currently
 5 got. But there are some newer treatments that
 6 have come out that are not quite doing that.
 7 **MS RICHARDS:** You've alluded to this already but
 8 there are two broad concepts of a treatment
 9 programme: preventative prophylactic treatment
 10 which, as you've described in your report, might
 11 be long-term, particularly for someone who is
 12 classed as a severe haemophiliac, or might be
 13 short-term because surgery is planned; and then
 14 on-demand or reactive treatment which responds
 15 to there being a bleed. Is that broadly
 16 accurate?
 17 **DR TUNSTALL:** Yes.
 18 **MS RICHARDS:** Sir, I note the time.
 19 **SIR BRIAN LANGSTAFF:** Yes, I just wonder if
 20 Professor Rockstroh would like to add anything
 21 to what has just been said over the last
 22 20 minutes or so?
 23 **MS RICHARDS:** Professor Rockstroh, before we rise,
 24 is there anything further you'd like to add at
 25 this stage?

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1 briefly what that is, what treatment you would
 2 typically expect a severe haemophiliac child to
 3 receive?
 4 **DR TUNSTALL:** So we're actually in a little bit of
 5 flux at the moment, but I can -- the standard of
 6 care would be -- for a child with severe
 7 haemophilia would be to start preventative
 8 treatment with recombinant Factor VIII, at or
 9 before their first joint bleed. So typically we
 10 look at times when the child is going to become
 11 more mobile and more at risk of bleeding into
 12 a joint, so that can be around the age of
 13 one year. And in general, we try and prevent
 14 them having joint bleeds. As we talked before,
 15 that any joint bleeds can lead to damage, our
 16 feeling, certainly, as an institution, is the
 17 earlier we start the better. But there's an
 18 element of compromise. Often we need to insert
 19 a central venous catheter to give regular
 20 treatment, getting access to veins. Factor VIII
 21 can only be given into veins and getting access
 22 to veins in small babies is difficult. So the
 23 compromise measure is to start around a year,
 24 sometimes ten months, sometimes a bit after
 25 a year.

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

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

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

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

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

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

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

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

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

20 **MS RICHARDS:** Dr Gooding?

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

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

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

13 They typically occur within the first
 14 20 exposures to Factor VIII, and typically occur
 15 fairly early on. So they typically occur in
 16 babies or young children. And they are
 17 a significant problem in haemophilia care.

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

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

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

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

16 **DR TUNSTALL:** Yes.

17 **MS RICHARDS:** How does that work?

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

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

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

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

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

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

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

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

12 **DR TUNSTALL:** Yes.

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

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

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

4 **DR TUNSTALL:** Um --

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

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

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

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

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

25 **DR TUNSTALL:** Albumin is a major constituent of --

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1 it's a protein in the blood, in the blood
 2 plasma. For extraction purposes, I think a lot
 3 of the recombinant products would need to use
 4 some human proteins just to stabilise and
 5 extract the Factor VIII from the cell line.
 6 There are some newer products which don't use
 7 human albumin. Clearly, it's not being the --
 8 the Factor VIII itself, it's not being extracted
 9 from plasma, and therefore we feel there should
 10 be a dramatically increased risk of viral
 11 transmission, we still think that the risk of
 12 viral transmission with recombinant Factor VIII
 13 should be vanishingly small, but because there
 14 are some human proteins involved in the
 15 manufacturing and some cases, then saying it's
 16 completely zero is beyond us.
 17 **MS RICHARDS:** What considerations would you have
 18 regard to in deciding how much treatment is
 19 required to be effective for an individual?
 20 What do you look at about the individual in
 21 assessing the treatment you give?
 22 **DR TUNSTALL:** Haemophilia care is quite standardised
 23 in the UK particularly. We have certain
 24 guidance. We plan treatment as a national body,
 25 through the UKHCDO, and -- and look at guidance

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1 **SIR BRIAN LANGSTAFF:** So it's per kilo?
 2 **DR TUNSTALL:** Yeah. It's still -- Factor VIII in
 3 general, there's a certain element of giving
 4 best bang for buck. That it's been expensive
 5 resource. So we're looking at effective dosing
 6 but it's not dosing to try and normalise factor
 7 levels, it's dosing to try to achieve factor
 8 levels that we know will prevent a certain
 9 amount of bleeding.
 10 Whether that could still be improved, a lot
 11 of us argue we should still be giving more but
 12 we start at a basic dose per kilo.
 13 **DR GOODING:** Just one extra thing with that, we do
 14 some monitoring tests as well, so -- as you've
 15 touched on already, but there are some --
 16 there's some new software that can be used to --
 17 to look at the response to treatment, so you can
 18 check a level sort of pre-dose and then
 19 after dose and then maybe a few hours later and
 20 then generate what we call a pharmacokinetic
 21 profile so you can actually graphically
 22 represent what the Factor VIII level is likely
 23 to be after a dose and when it might drop down
 24 to, say, 5 per cent, 3 per cent, 1 per cent, and
 25 maybe give a dose -- the next dose just ideally,

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1 which is written by the UKHCDO, and -- so within
 2 that there are certain parameters on starting
 3 treatment. So it -- it lays out -- in the
 4 UKHCDO prophylaxis guidance it lays out what
 5 would be a reasonable starting dose.
 6 That dose would then be adjusted according
 7 to different parameters, basically, to the
 8 response to treatment, and the response to
 9 treatment would be based on bleeding levels,
 10 also baseline Factor VIII, measuring the levels
 11 and seeing if we're getting the expected target
 12 levels of Factor VIII.
 13 We may adjust it, we are constantly looking
 14 at -- for example, in children, which is my
 15 area, that we'll be looking at their joints,
 16 looking at their activity, looking at any
 17 problems they may have, and looking for any
 18 signs that the treatment is inadequate or not
 19 working perfectly for them and adjusting on the
 20 basis of that.
 21 **SIR BRIAN LANGSTAFF:** By "reasonable starting dose",
 22 presumably you don't give the same reasonable
 23 starting dose to a small young child as you
 24 would to a large, big adult?
 25 **DR TUNSTALL:** On a per kilo basis.

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1 I suppose, around the 3 to 1 per cent mark so
 2 it's both effective and efficient in a sense.
 3 **SIR BRIAN LANGSTAFF:** Plainly the difference between
 4 somebody being given Factor VIII or making it
 5 themselves is that when they make it themselves,
 6 it's a constant process --
 7 **DR GOODING:** (Nodded).
 8 **SIR BRIAN LANGSTAFF:** -- and they constantly
 9 maintain whatever the level may be.
 10 **DR GOODING:** Yes.
 11 **SIR BRIAN LANGSTAFF:** If you give Factor VIII, is
 12 there a half life? Is that how it's put?
 13 **DR GOODING:** Yes.
 14 **DR TUNSTALL:** Yes.
 15 **SIR BRIAN LANGSTAFF:** But what you're saying is that
 16 will differ from person to person?
 17 **DR GOODING:** Yes, so typically it's much shorter in
 18 young children and it often gets to around about
 19 12 hours or something like that, but it does
 20 depend on the product that's being
 21 given because -- we may come on this in
 22 a minute, but the -- there are some newer
 23 extended half-life products so there's ways of
 24 lengthening the half life, and then we would use
 25 that, that monitoring technique, just to see

<p style="text-align: right;">61</p> <p>1 what happens. But there is a big variability</p> <p>2 between individuals, and so that's where that --</p> <p>3 that sort of measuring step comes in.</p> <p>4 DR TUNSTALL: I mean, just to say on that that if</p> <p>5 you're producing Factor VIII yourself, then, as</p> <p>6 you say, you get a constant level more and more,</p> <p>7 but -- but the curve is a decay curve so if we</p> <p>8 give a dose of Factor VIII you get a high point</p> <p>9 at the level that it's given and then it</p> <p>10 decreases quite rapidly down until it's really</p> <p>11 a very low level towards the end --</p> <p>12 SIR BRIAN LANGSTAFF: You spoke --</p> <p>13 DR TUNSTALL: -- (overspeaking) --</p> <p>14 SIR BRIAN LANGSTAFF: -- about a baseline level</p> <p>15 earlier, is that the lowest to which you want it</p> <p>16 to drop?</p> <p>17 DR TUNSTALL: The baseline level that we'd normally</p> <p>18 talk about is what -- is the baseline of</p> <p>19 endogenous Factor VIII, so that might be</p> <p>20 effectively zero for a -- for someone with</p> <p>21 severe haemophilia A. We talk about trough</p> <p>22 levels and trough levels are, again, an area</p> <p>23 where there are different beliefs, but we know</p> <p>24 fairly well that if you have a trough level that</p> <p>25 spends a prolonged period of time below 1</p>	<p style="text-align: right;">62</p> <p>1 per cent or below 3 per cent or, you know, the</p> <p>2 longer time you spend lower down there, then the</p> <p>3 higher the risk of bleeding. So we want to</p> <p>4 maintain good trough levels, and that's</p> <p>5 a fundamental part of the care.</p> <p>6 MS RICHARDS: You've described in terms of frequency</p> <p>7 of treatment in your statement that when a child</p> <p>8 with severe haemophilia starts on this</p> <p>9 prophylaxis programme, it'll be three to four</p> <p>10 Factor VIII treatments a week, on average,</p> <p>11 subject to extended half life recombinant which</p> <p>12 will make it less frequent.</p> <p>13 DR TUNSTALL: So normally every other day. Every</p> <p>14 48 hours is our -- is our standard starting</p> <p>15 regimen.</p> <p>16 MS RICHARDS: Is that something that continues at</p> <p>17 that frequency, potentially lifelong, or are you</p> <p>18 able to achieve longer periods between</p> <p>19 treatments?</p> <p>20 DR TUNSTALL: In the absence of using extended half</p> <p>21 life products, then certainly in paediatric care</p> <p>22 we'd never recommend going beyond two days.</p> <p>23 Sometimes we end up giving daily treatment.</p> <p>24 If -- if the levels aren't good enough or the</p> <p>25 control isn't good enough with every other day</p>
<p style="text-align: right;">63</p> <p>1 dosing.</p> <p>2 DR GOODING: That will be similar for the adult</p> <p>3 practice as well, really.</p> <p>4 MS RICHARDS: And the extended half life recombinant</p> <p>5 Factor VIII may enable you to extend it to about</p> <p>6 every three days; is that right?</p> <p>7 DR TUNSTALL: Yes, on average they -- they give</p> <p>8 about a 50 per cent extension of the half life,</p> <p>9 so on average if you gave a certain dose every</p> <p>10 two days of the standard molecule, you could</p> <p>11 probably give the same dose and achieve similar</p> <p>12 levels if you give it every three days, but</p> <p>13 that's on average and there's a lot of</p> <p>14 inter-individual variation.</p> <p>15 MS RICHARDS: And then can we look just shortly at</p> <p>16 some of the other treatments that are still used</p> <p>17 for haemophilia A.</p> <p>18 DDAVP, which we know has been around since</p> <p>19 the second half of the 1970s, that's a synthetic</p> <p>20 analogue of a naturally occurring hormone</p> <p>21 vasopressin; is that right?</p> <p>22 DR TUNSTALL: That's right, yes.</p> <p>23 MS RICHARDS: And that will increase the level of</p> <p>24 Factor VIII?</p> <p>25 DR TUNSTALL: So that tends to increase the levels</p>	<p style="text-align: right;">64</p> <p>1 of Factor VIII if there is some Factor VIII to</p> <p>2 increase the levels of. Obviously for somebody</p> <p>3 not producing any Factor VIII, then Desmopressin</p> <p>4 and DDAVP is not likely to be effective. It</p> <p>5 causes release of the (inaudible) factor and</p> <p>6 Factor VIII from the endothelium, from the</p> <p>7 lining of the blood vessels, and you get an</p> <p>8 increase. It's very variable between</p> <p>9 individuals but, on average, maybe about four</p> <p>10 times the baseline levels.</p> <p>11 So if somebody had levels of 20, then they</p> <p>12 might go up to 80. But then we'll reduce them</p> <p>13 down.</p> <p>14 MS RICHARDS: So it's typically used for those with</p> <p>15 mild haemophilia or von Willebrand?</p> <p>16 DR TUNSTALL: Yes.</p> <p>17 MS RICHARDS: It's not used for those with severe</p> <p>18 haemophilia; is that right?</p> <p>19 DR TUNSTALL: That's right.</p> <p>20 MS RICHARDS: What about moderate haemophilia?</p> <p>21 DR TUNSTALL: In general not in moderate haemophilia</p> <p>22 because normally if we're treating a bleed then</p> <p>23 we want to get levels higher than that.</p> <p>24 MS RICHARDS: And you've said in your report it's</p> <p>25 not usually used for prolonged periods of time;</p>

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1 why is that?

2 **DR TUNSTALL:** There's a blunting of the effect, so

3 when you give the first dose, you get more

4 release and a higher peak, and with subsequent

5 doses you get a -- diminishing returns.

6 There's also concern about some of the

7 side effects. So this is a physiologically

8 active analogue, one of the things it does is

9 cause fluid retention and disturbances of

10 electrolytes, things like the sodium levels in

11 the body, which can cause problems. And if you

12 treat for a prolonged period of time you're more

13 likely to run into problems too.

14 **MS RICHARDS:** But it's an effective treatment for

15 those who don't require long-term prophylactic

16 treatment?

17 **DR TUNSTALL:** It can be a very effective treatment,

18 yes. It's situation-specific, and I think in

19 the context of life threatening bleeding then

20 we'd almost always be using a factor

21 concentrate, but, but it depends on the

22 situation. And it can be adequate for covering

23 surgery, depending on the patient and the

24 situation.

25 **MS RICHARDS:** Would you normally give a test dose

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1 internationally there is some thought that the

2 rates of inhibitor formation are lower with

3 plasma-derived Factor VIII. There's a certain

4 amount of evidence but it's quite controversial,

5 and in the UK we've generally taken the view

6 that the downsides of plasma-derived Factor VIII

7 for primary prophylaxis outweigh the possible

8 upsides.

9 There's also evidence that in the context of

10 immune tolerance for inhibitors, when we keep on

11 giving the Factor VIII, sometimes it works

12 beautifully, sometimes it doesn't work. And

13 sometimes when it doesn't work we use extra

14 measures, and one of those measures has been to

15 try plasma-derived Factor VIII, and there's

16 certainly cases where if we give recombinant

17 Factor VIII immune tolerance and it doesn't

18 work, if we change to a plasma-derived

19 Factor VIII, it has worked, and it may well

20 be -- and I don't know in the detail of those --

21 it may well be that there were people who have

22 had inhibitors who have been tolerised with

23 a plasma-derived Factor VIII. In that case we

24 would stay on a plasma-derived Factor VIII.

25 **DR GOODING:** And it's worth noting that for immune

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1 before using it?

2 **DR TUNSTALL:** That's standard practice, yes.

3 **MS RICHARDS:** And why is that?

4 **DR TUNSTALL:** Just because of that variability in

5 response. And -- and knowing what levels of

6 response. There's variability in the -- the --

7 how long that's sustained for, both of which are

8 important information to know before going into

9 surgery, for example.

10 **MS RICHARDS:** Then plasma derived Factor VIII

11 concentrates, you say in your report rarely used

12 for haemophilia A in the UK. The figures that

13 you've drawn from the National Haemophilia

14 Database Annual Report show 13.4 million units

15 of plasma-derived Factor VIII used for

16 haemophilia A out of a total Factor VIII usage

17 of 600 million units. So a small proportion but

18 nonetheless not a vanishingly small one. When

19 and why would plasma-derived Factor VIII

20 concentrate still be used in modern practice?

21 **DR TUNSTALL:** To be honest, I don't know exactly

22 where those 13 million -- I could talk about

23 some of the places that we have used it. There

24 is a certain amount of evidence -- we talked

25 about inhibitors before, certainly

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1 tolerance reduction the amount of Factor VIII

2 that you give is quite high, so that could

3 explain -- I don't know, you know, for definite

4 that these units -- but that could explain why

5 there's a relatively high volume there.

6 **MS RICHARDS:** Then tranexamic acid.

7 **DR GOODING:** Shall I take this one?

8 **DR TUNSTALL:** Yes.

9 **DR GOODING:** So, tranexamic acid is a drug which

10 essentially stable -- allows clots to remain

11 stable without being broken down, so it's

12 a useful therapy for generally mild sort of

13 bleeding problems, particularly in the sort of

14 mucosal kind of tract, so if you're looking at

15 nosebleeds, gum bleeding, that sort of thing.

16 It's something we use if there's been that

17 kind of bleeding in severe haemophilia and it's

18 often used in mild haemophilia where, you know,

19 if you're going to have a procedure of some

20 sort, like a dental extraction, it could be very

21 useful in that sort of setting. It's also used

22 for heavy menstrual bleeding outside of the

23 setting of bleeding disorders because it helps

24 from that point of view as well. But it is used

25 very widely.

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1 **MS RICHARDS:** I want to turn to ask you a little
 2 about haemophilia B now.
 3 Now, haemophilia B is a deficiency of
 4 Factor IX. Again, could you just outline for us
 5 haemophilia B and how it might impact upon an
 6 individual and any material differences between
 7 haemophilia A and haemophilia B in that respect?
 8 **DR GOODING:** Severe -- haemophilia B is actually
 9 very similar in a lot of ways to haemophilia A,
 10 in that the bleeding manifestations are very
 11 similar. The severity levels that have been
 12 taken are very similar as well. There's some
 13 argument as to whether it may be slightly milder
 14 for some people but essentially the Factor VIII
 15 and IX in the clotting cascade work, you know,
 16 at a very similar sort of level. So the -- you
 17 can see why -- why they produce this -- the same
 18 sort of disease, phenotype. In terms of
 19 differences, well, the inheritance is very
 20 similar. The half life of Factor IX is slightly
 21 longer, so that's a difference when we come on
 22 to, sort of, therapeutics. But otherwise, they
 23 are, sort of, very similar, really, in terms of
 24 management as well.
 25 **MS RICHARDS:** And it's also classified, as

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1 and Factor XII, which less relevant. And so
 2 that -- in that respect, we would pick up
 3 haemophilia A, haemophilia B, and then take it
 4 from there.
 5 **MS RICHARDS:** Again, it's something that can occur
 6 within families or, as with haemophilia A, occur
 7 spontaneously?
 8 **DR GOODING:** Yes.
 9 **DR TUNSTALL:** Yes. Basically the way it's inherited
 10 it's a gene on factor -- on the X chromosome,
 11 and it's got the same patterns of inheritance.
 12 **MS RICHARDS:** Is there any material difference
 13 between haemophilia A and haemophilia B in terms
 14 of the risks without treatment and the way in
 15 which bleeds occur?
 16 **DR TUNSTALL:** Not clear differences, no. No.
 17 There's differences in treatment and response to
 18 treatment. There's difference in inhibitor
 19 rates and the patterns of inhibitors with
 20 haemophilia B, but as far as without treatment,
 21 then there are no significant differences.
 22 **MS RICHARDS:** And in terms of treatment in the case
 23 of those who develop inhibitors, FEIBA can be
 24 contraindicated; is that right?
 25 **DR TUNSTALL:** It's a relative contraindication. The

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1 I understand it, into severe, moderate and mild.
 2 **DR GOODING:** (Nodded)
 3 **MS RICHARDS:** Is it the same levels that are used
 4 for the classification as with factor
 5 (inaudible).
 6 **DR GOODING:** Yes, yes.
 7 **MS RICHARDS:** In terms of diagnosis, again,
 8 a similar --
 9 **DR TUNSTALL:** Very similar process, yes.
 10 **DR GOODING:** So the same blood test would be
 11 effectively -- you know, we talked about the
 12 prolongation of the APTT clotting time, so it's
 13 the same -- you see the same picture if you're
 14 doing a coagulation screen, you get this
 15 isolated -- the isolated prolongation of the
 16 APTT, and then, in the same sort of way, if
 17 you're suspecting a bleed, you'd go on and check
 18 that. So I suppose if you're looking at a newly
 19 diagnosed child, for example, with bleeding
 20 manifestations, the coagulation screen would be
 21 done, the APTT would found to be prolonged, and
 22 then typically what would happen from there is
 23 that you'd -- you'd actually do all the clotting
 24 factors that are affected. So within APTT we
 25 would check Factor VIII, Factor IX, Factor XI,

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1 problem with inhibitors in haemophilia B is they
 2 often take an allergic form and sometimes they
 3 can give rise to a very severe allergic
 4 reaction, what we call an anaphylaxis. The
 5 problem with FEIBA is it contains Factor IX. So
 6 for those who have got an inhibitor, it is still
 7 sometimes used in patients with inhibitors
 8 against Factor IX but it can cause problems.
 9 **MS RICHARDS:** But current treatments for haemophilia
 10 B, the primary treatment is recombinant
 11 Factor IX; is that right?
 12 **DR TUNSTALL:** Yes, so Desprovasin doesn't work, and
 13 we use tranexamic acid in a similar way. There
 14 is some use of plasma-derived Factor IX. The
 15 recombinant Factor IX is also used,
 16 plasma-derived Factor IX is probably in --
 17 I don't have the statistics to hand, but I'd
 18 imagine --
 19 **MS RICHARDS:** 4.5 million units out of a total usage
 20 of 80 million according to the last National
 21 Haemophilia Database report.
 22 **DR TUNSTALL:** Yes, so a bit higher. There are those
 23 who seem to respond better to plasma-derived
 24 Factor IX or to have better pharmacokinetics
 25 with plasma-derived Factor IX than with

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1 recombinant Factor IX.

2 **MS RICHARDS:** In terms of the recombinant Factor IX,

3 the frequency of injections can be less than the

4 frequency of injections with the Factor VIII?

5 **DR TUNSTALL:** That's right. It naturally has

6 a longer half-life, which means that in general

7 a standard dosing might be twice a week with

8 a standard molecule but it's also true the

9 extended half-life molecules are more extended

10 for the Factor IX than they are for Factor VIII.

11 In those cases weekly dosing is typical.

12 **MS RICHARDS:** You've said you can even achieve

13 fortnightly dosing in some cases?

14 **DR TUNSTALL:** Yes.

15 **MS RICHARDS:** Then haemophilia C, or Factor XI

16 deficiency. Could one of you just outline that

17 for us, please.

18 **DR GOODING:** So it's a sort of -- it is -- this is

19 a very different sort of situation, really. So

20 this is Factor XI deficiency. It's typically

21 characterised by more of a very variable

22 disorder, and so we don't see this sort of

23 correlation between factor levels and bleeding

24 phenotype, this sort of type of disorder you

25 get. So it's not like we can say, you know,

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1 **DR GOODING:** That's right.

2 **MS RICHARDS:** It's plasma-derived Factor XI

3 concentrate which is the mainstay of treatment

4 when it is required?

5 **DR GOODING:** Yes and very much when it is required.

6 So it is quite unusual to require a Factor XI

7 replacement in this sort of disorder. Most of

8 the time the bleeding phenotype is mild and

9 usually we would use adjunctive sort of measures

10 like tranexamic acid. The slight concern with

11 some of the concentrates there's been an

12 increased risk in thrombosis. So when it is

13 given, it's given in a very carefully considered

14 way and usually at a lowish dose.

15 **MS RICHARDS:** We can see from your report an idea of

16 the kind of figures of those who might receive

17 the Factor XI concentrate which is produced, as

18 I say, from human plasma. Forty-five patients

19 received Factor XI in the UK in 2018/19 which is

20 1.3 per cent of registered patients with

21 deficiency.

22 As well as tranexamic acid which you've

23 described as remarkably effective for Factor XI,

24 fresh frozen plasma is also used?

25 **DR GOODING:** That's right, yes, quite often I think

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1 these levels are less than 10 per cent or less

2 than 1 per cent. We're going to see joint

3 bleeding or bleeding problems, so we don't --

4 that's a really important difference with this

5 disorder and how it presents and then obviously

6 how it's treated.

7 We typically see a different sort of

8 bleeding pattern as well. Classically, it's

9 areas where there's a sort of what we call high

10 fibronetic activity. But typically we see,

11 I suppose, bleeding into the mouth or

12 mucosal-type bleeding. It can complicate

13 surgery as well. But it's not something that

14 tends to present with sort of spontaneous

15 bleeding into joints and muscles.

16 **MS RICHARDS:** You've said it's often asymptomatic

17 and most commonly problematic after surgery or

18 trauma, sometimes?

19 **DR GOODING:** Yes, that's fair to say, and we may see

20 it manifesting itself with heavy menstrual

21 bleeding or postoperative sort of bleeding.

22 **MS RICHARDS:** There's no recombinant Factor XI or

23 treatment for this condition?

24 **DR GOODING:** Yes.

25 **MS RICHARDS:** Is that right?

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1 because of those concerns about thrombosis.

2 **MS RICHARDS:** Then von Willebrand disease, can you

3 tell us what that is please.

4 **DR TUNSTALL:** Shall I take that?

5 **DR GOODING:** Yes.

6 **DR TUNSTALL:** Von Willebrand disease is a disorder

7 of the von Willebrand factor protein which is

8 a -- so it can either be low levels or low

9 functioning levels of von Willebrand factor.

10 Von Willebrand factor is quite central to

11 coagulation in two parts. It's involved in

12 platelet aggregation and adhesion, which is very

13 important for clotting, and it's important

14 because it stabilises Factor VIII in the

15 circulation.

16 It's classified in different ways: so a type

17 1 where you have reduced levels of

18 von Willebrand factor and reduced function with

19 those levels; type 2, where often as well as the

20 low levels, it doesn't function normally so

21 there's a mismatch between its activity and the

22 amount of the protein in the blood; and type 3,

23 where you have effectively undetectable levels.

24 Type 2 is further classified. There's type

25 2A and type 2N, where -- which are -- you

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

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

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

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

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

4 **DR TUNSTALL:** I don't know the proportions.

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

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

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

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

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

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

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

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

24 **DR GOODING:** Yes.

25 **MS RICHARDS:** Again, is this something that would

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

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

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

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1 in haemophilia A.

2 **MS RICHARDS:** Then inhibitors can occur with type 3

3 but not type 1 or 2?

4 **DR TUNSTALL:** Yeah, I don't know that they're

5 reported in type 1 or type 2. So yes, they do

6 occur at times in type 3.

7 **MS RICHARDS:** What's the primary treatment and the

8 approach to treatment for von Willebrand's?

9 **DR TUNSTALL:** Generally it's reactive rather than

10 preventative. Depending on the patterns of

11 bleeding. Even in type 3 von Willebrand's

12 disease, the patterns of bleeding are very

13 variable, and some people don't bleed to -- from

14 year to year, and so it tends to be managing

15 issues as they come up. Those issues may be

16 around recurrent nosebleeds, about bleeding from

17 the mouth. They may be around heavy menstrual

18 bleeding and managing that.

19 There's a number of issues, they may be more

20 trauma-related, so in response to injury or

21 covering surgery or dental procedures, so it's

22 depending on the situation.

23 **MS RICHARDS:** If treatment is required, is it most

24 likely to be DDAVP or tranexamic acid or

25 something else?

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1 treatment we don't use DDAVP in that sort of

2 setting. So typically after the age of maybe

3 two or three years it's felt safe but before

4 that, because of the changes with fluid

5 retention, there's a risk, particularly, of

6 sodium levels dropping and causing fits and

7 seizures, so we don't tend to use it in that --

8 so if there is a need for treatment in that

9 group, they tend to have the plasma-derived

10 von Willebrand concentrate, then after that we

11 would do the DDAVP tests and use that more

12 often.

13 **MS RICHARDS:** You've drawn attention in your report

14 to particular problems that women, and I should

15 make clear, women will suffer from

16 von Willebrand's, (*Witness nodded*) is it equally

17 as much as men or is it more women than men?

18 **DR GOODING:** The same.

19 **DR TUNSTALL:** One would predict equal numbers but

20 possibly reflecting that there are particular

21 difficulties for women with von Willebrand

22 disease. There are more women registered in the

23 UK with von Willebrand disease than men.

24 **MS RICHARDS:** And the particular problems they can

25 experience can be related to menstrual bleeding?

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1 **DR TUNSTALL:** Well, depending on the levels. So

2 again, it depends on the baseline levels, and

3 the baseline activity of the von Willebrand

4 factor, and it depends on the situation as to

5 whether DDAVP or tranexamic acid, or factor

6 concentrate, so factor concentrate would be

7 often talked about plasma-derived Factor VIII

8 also contained von Willebrand factor. They vary

9 slightly in how much von Willebrand factor they

10 contain but there are products that are

11 particularly designed and marketed as for

12 treatment of von Willebrand factor, and they're

13 used.

14 **MS RICHARDS:** So there's no recombinant equivalent

15 for VW?

16 **DR TUNSTALL:** There is a recombinant von Willebrand

17 factor that's just come to the market now. It

18 is not licensed for prevention or licensed in

19 children and I don't think it's yet funded in

20 the NHS, but it's recently been developed and so

21 we don't quite know how that's going to fit in,

22 and where it will be most used.

23 **DR GOODING:** Just one thing about treatment as well

24 is that in the paediatric cohort, if a child

25 with more severe von Willebrand disease needs

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1 **DR TUNSTALL:** Menstrual bleeding can be a big

2 problem in von Willebrand's disease, yeah.

3 **MS RICHARDS:** And pregnancy. There can be a severe

4 drop-off in VWF levels after delivery and a risk

5 of post-partum haemorrhage.

6 **DR TUNSTALL:** Yes.

7 **DR GOODING:** Yes.

8 **MS RICHARDS:** There's a handful of more general

9 questions I have about bleeding disorders,

10 rather than specific to the four that we've

11 looked at.

12 Life expectancy, so I'm not asking you to

13 comment upon life expectancy for those with

14 hepatitis C or HIV, we've heard some evidence

15 from others in relation to that but just

16 generally in terms of life expectancy nowadays

17 for somebody with any of the forms of

18 haemophilia or von Willebrand that we've

19 discussed. What's known about that?

20 **DR GOODING:** I think typically we would expect life

21 expectancy to be approaching normal now. The --

22 I suppose having inhibitors may affect life

23 expectancy but, essentially, my feeling is that

24 we're seeing patients with or people with

25 haemophilia, rather, growing into an older age,

<p style="text-align: right;">85</p> <p>1 and that's evidenced by the fact that we're</p> <p>2 starting to see some of the diseases of older</p> <p>3 age as well, and that's an area of particular</p> <p>4 interest to some clinicians now.</p> <p>5 MS RICHARDS: Does having a bleeding disorder impact</p> <p>6 upon a person's susceptibility to infection more</p> <p>7 generally, as far as you know?</p> <p>8 DR TUNSTALL: I don't think we've found clear</p> <p>9 evidence to that, no. I mean there is</p> <p>10 theoretical considerations that the clotting</p> <p>11 system and the immune system are not entirely</p> <p>12 disconnected but I don't know of any clear</p> <p>13 evidence to suggest that.</p> <p>14 DR SEKHAR: If may add.</p> <p>15 MS RICHARDS: Yes, absolutely.</p> <p>16 DR SEKHAR: Because bleeding, when you say bleeding</p> <p>17 disorder, we've been talking so far about</p> <p>18 inherited conditions but when people have severe</p> <p>19 bleeding and they are given blood transfusions,</p> <p>20 there is some suggestion that blood</p> <p>21 transfusions, especially red blood cell</p> <p>22 transfusions, can affect a person's immune</p> <p>23 system and it's easier to acquire infections.</p> <p>24 It's relatively new areas in the literature.</p> <p>25 MS RICHARDS: Thank you. Can I just explore in</p>	<p style="text-align: right;">86</p> <p>1 relation to haemophilia, some issues relating</p> <p>2 specifically to women. What's the difference</p> <p>3 between someone with haemophilia and</p> <p>4 a symptomatic carrier? Is there in truth</p> <p>5 a difference?</p> <p>6 DR TUNSTALL: Not in my opinion. A symptomatic</p> <p>7 carrier has often been used, I don't know why we</p> <p>8 use that terminology particularly, but there are</p> <p>9 women who have low Factor VIII levels, therefore</p> <p>10 they have haemophilia in my view.</p> <p>11 DR GOODING: That would be my opinion as well,</p> <p>12 actually.</p> <p>13 MS RICHARDS: Thank you. Then I've just -- some</p> <p>14 questions about aspects of modern haemophilia</p> <p>15 care. Am I right in thinking it's still</p> <p>16 organised through Haemophilia Centres?</p> <p>17 DR GOODING: Yes.</p> <p>18 MS RICHARDS: And it's a form of specialised care,</p> <p>19 and you've referred already to some of the</p> <p>20 standards that are set for haemophilia care</p> <p>21 through UKHCDO. I wanted to look at a couple of</p> <p>22 aspects of a set of quality standards.</p> <p>23 Henry, could we have EXPG0000029, please.</p> <p>24 These are described as:</p> <p>25 "Quality standards, care of people with</p>
<p style="text-align: right;">87</p> <p>1 inherited and acquired haemophilia and other</p> <p>2 bleeding disorders, July 2018."</p> <p>3 I think we've discussed this before you've</p> <p>4 come in, you're broadly familiar with this</p> <p>5 document. There were two aspects of it that</p> <p>6 I wanted to ask you about so if we could go,</p> <p>7 please, Henry to page 12.</p> <p>8 DR TUNSTALL: Is it worth contextualising what these</p> <p>9 standards are?</p> <p>10 MS RICHARDS: Yes, please. Yes.</p> <p>11 DR TUNSTALL: One of the processes of ensuring good</p> <p>12 care for people with haemophilia is a process of</p> <p>13 what we call peer review, whereby each centre,</p> <p>14 so Haemophilia Centres are organised into what</p> <p>15 we call comprehensive care centre, which would</p> <p>16 be a specialist regional centre, and then</p> <p>17 haemophilia care -- haemophilia centres who will</p> <p>18 manage the day-to-day care of patients who are</p> <p>19 closer to that town, but usually will be linked</p> <p>20 in with a comprehensive care centre, and there</p> <p>21 is a peer review process where clinicians from</p> <p>22 different centres go and assess the care of</p> <p>23 people with inherited bleeding disorders in</p> <p>24 different centres, against different criteria,</p> <p>25 and these are the criteria that are used.</p>	<p style="text-align: right;">88</p> <p>1 MS RICHARDS: Are these standards that every</p> <p>2 comprehensive care centre is expected to meet in</p> <p>3 every respect or are they more aspirational?</p> <p>4 DR TUNSTALL: Without pre-judging the results of the</p> <p>5 recent round of peer review I don't imagine any</p> <p>6 centre reached every standard, and some of them</p> <p>7 are probably more aspirational than ...</p> <p>8 MS RICHARDS: I'm going to ask you about two aspects</p> <p>9 of them, so if we go to the bottom of page 12,</p> <p>10 please, Henry. Thanks.</p> <p>11 We've got a heading:</p> <p>12 "Staffing levels and skill mix."</p> <p>13 If you look down towards the very bottom of</p> <p>14 the page we have (e):</p> <p>15 "Clinical or counselling specialist</p> <p>16 psychologist or appropriately trained</p> <p>17 psychotherapist."</p> <p>18 So this sets out -- I use the words</p> <p>19 relatively an aspiration or a standard that</p> <p>20 staffing should include, amongst the other</p> <p>21 specialities that are set out there,</p> <p>22 a specialist psychologist or psychotherapist.</p> <p>23 Two questions arising from that, first of</p> <p>24 all, do you have any sense as to the extent to</p> <p>25 which that's achieved in practice in Haemophilia</p>

<p style="text-align: right;">89</p> <p>1 Centres?</p> <p>2 DR TUNSTALL: Yeah, I suppose on the use of term</p> <p>3 "aspirational", I'm just going to slightly roll</p> <p>4 back. I think it is laying down what we think</p> <p>5 should happen. That doesn't mean that every</p> <p>6 centre is able to do that and whether the</p> <p>7 funding is in place for every centre to do that</p> <p>8 is right.</p> <p>9 DR GOODING: It's useful to have a framework like</p> <p>10 this set out by the UKHCDO so we can then say to</p> <p>11 our hospital, I can say to my boss, "Actually,</p> <p>12 I need this", and then we can try and work</p> <p>13 towards having the things that we may not</p> <p>14 currently have to provide this standard.</p> <p>15 I suppose, yeah, but ...</p> <p>16 DR TUNSTALL: So we have a psychologist very much</p> <p>17 embedded within the multi-disciplinary team</p> <p>18 treating -- looking after families with children</p> <p>19 with haemophilia and it's a vital part of the</p> <p>20 service, we think. I don't think -- I'm fairly</p> <p>21 sure not every centre has the same access to</p> <p>22 psychologists.</p> <p>23 MS RICHARDS: Would you expect the focus of the</p> <p>24 psychology expertise that might be delivered in</p> <p>25 those centres which do have a psychologist to be</p>	<p style="text-align: right;">90</p> <p>1 counselling and support in relation to</p> <p>2 haemophilia and other bleeding disorders, or</p> <p>3 would you expect them to be able to provide</p> <p>4 specialist psychological support in relation to</p> <p>5 hepatitis or HIV?</p> <p>6 DR TUNSTALL: In general, speaking for our service,</p> <p>7 that they will try and support any aspects of</p> <p>8 care. But sometimes, when there's interaction</p> <p>9 with other services, then it may be that there</p> <p>10 is more specialist provision within those other</p> <p>11 services. So we wouldn't necessarily expect</p> <p>12 that our clinical psychologist would be an</p> <p>13 expert per se in issues relating to hepatitis or</p> <p>14 HIV, but would be an expert in dealing with</p> <p>15 psychological trauma and having expertise in</p> <p>16 different modalities which may well be</p> <p>17 applicable, or be able to tie in with</p> <p>18 signposting where there may be other support.</p> <p>19 But I think in general, my experience is</p> <p>20 that support from psychology services is very</p> <p>21 patchy, within the NHS in general.</p> <p>22 DR GOODING: Yes, I would agree with that. We have</p> <p>23 access to psychology services but we don't have</p> <p>24 a specialist psychologist and I wouldn't expect</p> <p>25 them to have a great deal of experience with</p>
<p style="text-align: right;">91</p> <p>1 individual disease conditions or certainly not</p> <p>2 a combination, necessarily, of disease</p> <p>3 conditions.</p> <p>4 MS RICHARDS: Then before we break, sir, just one</p> <p>5 further question in relation to this document.</p> <p>6 If we go, please, Henry, to page 16, we can see</p> <p>7 at the top of the page under the heading</p> <p>8 "Specialist services" it refers to:</p> <p>9 "Timely access to the following specialist</p> <p>10 staff and services should be available as part</p> <p>11 of an HCC service. HC should be able to access</p> <p>12 these services through network arrangements and</p> <p>13 we see a range of different types of specialist</p> <p>14 service including at J HIV services and</p> <p>15 H hepatology."</p> <p>16 As I understand this document, please</p> <p>17 correct me if I'm wrong, what this is envisaging</p> <p>18 is that where you have a patient under the care</p> <p>19 of your centre, who may have needs that fall</p> <p>20 within any of these areas, you would expect to</p> <p>21 be able, as it were, to make a referral or put</p> <p>22 them in touch with the relevant specialists.</p> <p>23 You wouldn't be offering those specialist</p> <p>24 services yourself?</p> <p>25 DR TUNSTALL: That's correct. More than that, we</p>	<p style="text-align: right;">92</p> <p>1 would expect some kind of relationship and</p> <p>2 communication with those services, to facilitate</p> <p>3 the particular care that our patient group would</p> <p>4 need.</p> <p>5 SIR BRIAN LANGSTAFF: I'm sorry, I interrupted.</p> <p>6 I beg your pardon.</p> <p>7 What this would mean would be, would it,</p> <p>8 that someone who was a haemophiliac who had HIV</p> <p>9 infection or hepatitis infection or both, could</p> <p>10 get the services of a psychologist who knew</p> <p>11 about haematology but not necessarily about HIV</p> <p>12 or hepatitis or could be referred to someone who</p> <p>13 is a psychologist working within the HIV and</p> <p>14 hepatology services -- hepatitis services who</p> <p>15 knew nothing very much about haematology?</p> <p>16 DR TUNSTALL: Talking about -- going back to the</p> <p>17 previous issue, I think it's possible they may</p> <p>18 have access to a psychologist with expertise in</p> <p>19 haematology but not HIV or hepatology. They may</p> <p>20 have access to a psychologist with expertise in</p> <p>21 hepatitis and HIV care. They may have access to</p> <p>22 both or they may have access to neither, and</p> <p>23 that's where I mean it's extremely patchy and</p> <p>24 I don't think -- different centres organise</p> <p>25 services in different ways, and many services</p>

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1 don't really have access at all or only have
 2 access to a general provision which is often
 3 after a very long wait.
 4 **MS RICHARDS:** This particular standard is not, in
 5 fact, concerned with psychology as such but
 6 concerned with those who might need care for
 7 their HIV or their liver. You would not be
 8 providing that or treatment in relation to that
 9 within the modern Haemophilia Centre, but you
 10 may make specialist referrals and we see later
 11 on in this document there is a reference to the
 12 possibility of having multi-disciplinary
 13 clinics.
 14 **DR GOODING:** Yes.
 15 **DR TUNSTALL:** I think that's correct. There would
 16 either be an expectation of established pathways
 17 for referrals, for patients to access those
 18 services, or a joint clinic.
 19 **MS RICHARDS:** But you'd expect in the modern era
 20 treatment and care for HIV or hepatitis to be
 21 undertaken by specialists in those particular
 22 fields.
 23 **DR GOODING:** Yes.
 24 **DR TUNSTALL:** I would, yes.
 25 **DR GOODING:** I think it's worth noting here as well

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1 the amount or the structure of the haemoglobin
 2 that circulates in the red blood cells, and
 3 these disorders are genetically inherited, and
 4 probably have arisen over the years because they
 5 did confer a certain sort of resistance to
 6 malaria and that's why they're very common in
 7 parts of the world where malaria was or is very
 8 prevalent.
 9 So haemoglobin is carried in the -- it's got
 10 an iron-containing molecule and has these
 11 protein chains, and the thalassaemias are
 12 disorders that affect the production of the
 13 protein chains, whereas sickle cell disorders
 14 affect the actual type of haemoglobin. So they
 15 are different disorders and they have different
 16 clinical consequences.
 17 So I'll start with thalassaemia. So the
 18 thalassaemias affect, as I say, the protein
 19 component of haemoglobin. They are very
 20 prevalent. They are the commonest genetic
 21 disorders across the world. They're divided
 22 into the alpha thalassaemias and the beta
 23 thalassaemias, depending on which of the protein
 24 chains is involved, and the end result is you
 25 don't make enough haemoglobin and this results

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1 with specialist services, unlike perhaps
 2 psychology services, it would be unthinkable
 3 that a Haemophilia Centre wouldn't have access
 4 to HIV services and hepatology. That would be,
 5 you know, an absolute expectation.
 6 **MS RICHARDS:** Sir, is that a convenient point to
 7 stop?
 8 **SIR BRIAN LANGSTAFF:** Yes, it is. Two o'clock.
 9 We'll take break. Two o'clock.
 10 **(1.04 pm)**
 11 **(The luncheon adjournment)**
 12 **(2.05 pm)**
 13 **MS RICHARDS:** I'm going to move on to ask the panel
 14 to consider transfusion-dependent disorders, and
 15 in particular the inherited disorders of
 16 haemoglobin. Could I start by asking you
 17 perhaps to tell us what haemoglobin is and what
 18 these disorders -- what problems these disorders
 19 generally cause?
 20 **DR RYAN:** Okay, so haemoglobin is the substance in
 21 our red blood cells that carries oxygen around
 22 the body, and we -- so the haemoglobin -- so we
 23 need to -- to obviously provide oxygen. And we
 24 have a number of disorders that are very common
 25 across the world that affect the amount of -- or

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1 in anaemia and it results in very small red
 2 blood cells.
 3 Because of the -- there's hundreds of
 4 different types of mutation affecting the beta
 5 thalassaemias and therefore a very different
 6 range of clinical spectrum of anaemia and
 7 disorders. So the alpha thalassaemias are
 8 usually not too much of a problem clinically
 9 although in some parts of the world, for
 10 instance in south Asia, China, there is a sort
 11 of moderately severe form of alpha thalassaemia
 12 that can require transfusions, but the commonest
 13 type of thalassaemia we encounter here in the UK
 14 as serious thalassaemia are the
 15 beta thalassaemias.
 16 We can divide those thalassaemias into those
 17 that are severe enough to need blood transfusion
 18 and those that don't need blood transfusion.
 19 But, as I say, the genetic basis of this is very
 20 complicated and really a lot of it depends on
 21 the part of the world that you came from,
 22 although we see quite a big spread across the UK
 23 now.
 24 So the problems of thalassaemia are related
 25 to anaemia. If you don't have enough blood

<p style="text-align: right;">97</p> <p>1 cells, you're going to feel very tired. If 2 you're a child and you don't make enough 3 haemoglobin, you're not going to grow and 4 develop, and your bone marrow tries to 5 compensate by expanding, this causes expansion 6 of the bones and causes bone problems and sort 7 of a -- sort of skeletal enlargement, and 8 expands by -- the liver and the spleen expand as 9 well. 10 And generally if you're a child born with 11 severe thalassaemia, you don't grow and survive, 12 and without any kind of blood transfusion 13 treatment you would typically die in the first 14 decade of life. 15 The other problems that we see are related 16 to the iron overload. So we can treat 17 thalassaemia with regular blood transfusions but 18 each blood transfusion carries with it a certain 19 amount of iron, and the iron cannot be -- our 20 bodies cannot get rid of iron very easily. So 21 the iron is retained by tissues, and the iron 22 particularly is retained in the liver, and it is 23 retained in the heart, it also affects the 24 endocrine glands, and -- it really affects 25 a number of other organs in the body.</p>	<p style="text-align: right;">98</p> <p>1 So iron causes inflammation in excess, and 2 this leads to chronic liver disease, namely 3 liver cirrhosis, and increases the risk of liver 4 cancer. In the heart, excess iron can cause 5 heart failure and heart rhythm disturbances, and 6 excess iron in the endocrine glands causes 7 problems such as diabetes, low thyroid, failure 8 to grow and develop, et cetera. 9 So the problems are really both due to 10 anaemia and iron overload, and there is a sort 11 of mix of both of those which -- it varies from 12 individual to individual depending on the type 13 of thalassaemia they have, and the type of 14 treatment that they have as well. 15 So it's a chronic disorder. People who are 16 transfusion-dependent will normally need blood 17 transfusions every -- between every two and six 18 weeks. And they will need to take treatment 19 really from the first year or so of life with 20 iron collation treatment. These are drugs that 21 actually remove the iron from the blood. 22 And they will need to attend -- so, as 23 I say, for blood transfusions, and regular 24 clinic appointments and all sorts of specialist 25 investigations to monitor for the affects of</p>
<p style="text-align: right;">99</p> <p>1 iron overload. 2 So that's sort of thalassaemia in 3 a nutshell. Do you want me to proceed with 4 sickle? 5 MS RICHARDS: No, we'll come on to sickle cell in 6 a few minutes. Just a few further matters 7 arising in relation to thalassaemia. 8 There's a national haemoglobinopathy 9 registry. 10 DR RYAN: Yes. 11 MS RICHARDS: And you've recorded in the report that 12 as of September 2019 the numbers on that 13 registry were 1,921 with thalassaemia and, just 14 to complete the figures, for sickle cell, which 15 we'll discuss in a few minutes, 13,675. And 16 then some rare anaemias which we'll also come on 17 to later, 460, although that may be, as I 18 understand it, something of an underestimate. 19 Just in relation to thalassaemia, you've 20 also said that those who will require regular 21 blood transfusions is in the region of, I think, 22 900 to 1,000. And that's a lifelong 23 requirement, is it? 24 DR RYAN: Yes, yes. But many patients who don't 25 require regular transfusions from childhood may</p>	<p style="text-align: right;">100</p> <p>1 start to need transfusions in adult life for 2 a variety of reasons. I think over the years we 3 have intended to lower our threshold for 4 transfusion because we have better drugs to 5 remove iron, and we realise that chronic anaemia 6 is really quite disabling for thalassaemia 7 patients. 8 MS RICHARDS: And we know from evidence that we've 9 heard that people with thalassaemia who received 10 regular transfusions developed hepatitis C. Is 11 there any data of which you're aware which tells 12 us how many were affected in that way? 13 DR RYAN: No, I think is the answer. I did -- I did 14 try and make enquiries to see whether we had 15 that information, but I don't think we do. But 16 the problem is that a lot of -- we have a lot of 17 patients arriving in the UK from abroad who 18 acquired hepatitis abroad and we don't, 19 therefore, know how long they've had it, how 20 they acquired it, and we don't know -- we 21 haven't really got reliable data on -- on deaths 22 from -- deaths from sort of iron overload as 23 opposed to other causes of liver disease. So -- 24 so we don't really -- in a nutshell, we don't 25 have that information although we are sort of</p>

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1 starting to collect it now.

2 **MS RICHARDS:** And you described symptoms associated

3 with either thalassaemia or the iron overload,

4 consequences of thalassaemia, fatigue and so on,

5 which obviously may be very similar to the

6 symptoms that an individual might experience

7 with hepatitis C. Do you know whether there

8 were problems of delays in people being

9 diagnosed with hepatitis C because they didn't

10 know that their symptoms were attributable or

11 might be attributable to something other than

12 their iron overload?

13 **DR RYAN:** I don't know for a fact. I would imagine

14 that that is the case. Hepatitis C screening of

15 blood only came in in the early 1990s. We knew

16 patients had chronic hepatitis but we didn't

17 know to what extent the iron in the liver was

18 contributing. So it wasn't very clear because

19 there's a number of mechanisms of liver disease

20 in thalassaemia.

21 **MS RICHARDS:** And the risk of a person with

22 thalassaemia and chronic viral hepatitis

23 developing liver cancer is, as I understand it,

24 compounded by the problems of iron overload?

25 **DR RYAN:** Absolutely, yes. Yes.

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1 haemoglobin, and we have a gene therapy, it's --

2 and a new exciting prospect for thalassaemia

3 which is under consideration at the moment.

4 **MS RICHARDS:** Then are there particular difficulties

5 for someone with thalassaemia who has

6 hepatitis C, or indeed HIV, that are

7 compounded -- other than the liver consequences

8 we've discussed, that are compounded?

9 **DR RYAN:** Well, I've never seen a thalassaemia

10 patient with HIV. Whenever we get a patient

11 with hepatitis C, and we do still see patients

12 as they arrive from other parts of the world,

13 they are managed with the liver teams, as in the

14 other disorders. The treatment itself can

15 compound the fatigue that they get and also some

16 of the older treatments used to increase the

17 amount of haemoglobin so they would end up

18 needing more blood transfusion.

19 **MS RICHARDS:** Can I ask you to turn to sickle cell

20 disorders and tell us a little bit more about

21 those?

22 **DR SEKHAR:** Can I just comment?

23 A really important part of thalassaemia is,

24 as Kate was saying, to get rid of the iron, and

25 until a few years ago it was mainly injections,

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1 **MS RICHARDS:** Which can result in fibrosis,

2 cirrhosis and cancer?

3 **DR RYAN:** Mm-hm.

4 **MS RICHARDS:** Is there any data about the impact on

5 life expectancy for a hepatitis C positive

6 individual with thalassaemia against someone who

7 has thalassaemia but no hepatitis?

8 **DR RYAN:** I don't know of any UK data. I think

9 there will be data from other parts of Europe

10 where hepatitis C is much more prevalent.

11 The life expectancy of thalassaemia is

12 changing all the time because we now have much

13 better ways of treating iron overload and we are

14 much more able to assess more accurately how

15 much iron is in the body through imaging

16 scanning, so we're much better at treating iron

17 overload. So we think our life expectancy for

18 our thalassaemia patients is -- you know,

19 providing they take the treatment, should be

20 approaching, you know, near normal now. There

21 are other treatments coming on board for

22 thalassaemia as well.

23 **MS RICHARDS:** That are not transfusion dependent?

24 **DR RYAN:** Yeah. So there are -- we're on -- we have

25 new drugs in development that will improve the

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1 subcutaneous injections, which had to be

2 injected at night, or during the day, but kept

3 going, as a syringe, for the best part of

4 8 hours or so. For young people, it was very

5 difficult. So compliance was very difficult,

6 and going to college or uni or senior school was

7 very difficult. So many of them have now been

8 able to move on to oral chelation but even that

9 is fraught with a lot of --

10 **DR RYAN:** Adherence is still a big issue. The drugs

11 themselves are mostly non-toxic but they need

12 monitoring, but I think with any chronic

13 disease, adherence is -- is an issue, for

14 patients.

15 **MS RICHARDS:** And the point you've just made adds to

16 the treatment burden for the patient.

17 **DR RYAN:** Yes.

18 **MS RICHARDS:** We discussed that in other contexts

19 but if you are a patient with thalassaemia who

20 is having also to be treated for the

21 consequences of iron overload and having to

22 receive what we know were horrific treatments in

23 terms of side effects for hepatitis C, prior to

24 the modern era of treatment, that can be

25 a significant physical and psychological burden

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1 for the individual.

2 **DR SEKHAR:** Plus the monthly blood transfusions.

3 **MS RICHARDS:** Of course.

4 **DR RYAN:** I mean, there is -- there has been some

5 recent study which is looking at the real life

6 experience in -- and it shows that the quality

7 of life is -- is about 65 per cent. If you look

8 at quality of life indicators, it's about 65%

9 for thalassaemia patients compared to a normal

10 population, and that's even with safe blood

11 transfusion, reasonably, you know, effective

12 chelation. So it's still -- it is

13 a considerable psychological burden.

14 **MS RICHARDS:** And that's before you add the burden

15 of hepatitis C treatment?

16 **DR RYAN:** Yes.

17 **MS RICHARDS:** Sickle cell disorders.

18 **DR RYAN:** Sickle cell disorders refer to a group of

19 conditions where the basic problem is a mutation

20 in the haemoglobin molecule to produce

21 a substance called haemoglobin S. And

22 haemoglobin S, under certain conditions of low

23 oxygen or other conditions, causes the red

24 cell -- precipitates, if you like, in the red

25 cell and deforms the red cell into

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1 can be affected. You can divide the problems

2 into acute problems or chronic problems. So the

3 acute problems, I think the single most

4 difficult problem for patients is episodes of

5 pain, called the painful crisis. These are --

6 can occur very frequently in some patients, and

7 cause excruciating pain in different parts of

8 the body. And often the pain is -- it will

9 require strong painkillers, including morphine.

10 Patients need to be hospitalised for pain

11 management.

12 That is very variable. The number of crises

13 a patient gets is very variable, it can be none

14 a year, but most people will get episodes of

15 pain of varying severity, and some patients can

16 be in hospital 20 times a year for a painful

17 crisis.

18 Patients with sickle cell are anaemic. They

19 run a haemoglobin a lot lower than a normal

20 haemoglobin, and this can be made worse during

21 a crisis or during an infection. They're very

22 prone to infections as well because the spleen,

23 which is important for processing bugs, doesn't

24 work in sickle cell. So infection, particularly

25 with certain bacteria, is a big problem. And

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1 a characteristic sickle shape. And these

2 deformed red cells are not very pliable, they

3 don't pass through vessels very easily, so they

4 block vessels, and they cause inflammation and

5 they cause all sorts of problems.

6 Now, it's -- the sickle disorders really --

7 we refer to sickle cell disease, which is

8 a number of different types of sickle cell. The

9 most common in the UK is what we call SS, which

10 is about two-thirds of patients, and the rest

11 are SC -- SC, a mixture of other genetic

12 problems.

13 Sickle cell gene has arisen in Africa, so

14 most of our patients with sickle cell are of

15 African origin, either black African,

16 black British, black Caribbean, and that's about

17 two-thirds of the patients. The sickle cell

18 gene is also, however, found in the Middle East,

19 parts of southern Europe, and in parts of India

20 as well. So it's a sort of -- a disease that

21 affects predominantly non-Caucasians, but

22 increasingly it's seen in all different ethnic

23 groups.

24 So the problems of sickle cell, it's

25 a multi-system disease, and any part of the body

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1 malaria is a big problem as well.

2 And another major problem for children is

3 stroke. So about 10% of sickle children will

4 get an overt stroke, with about another 20% of

5 sickle children getting, sort of, brain

6 infarcts, which may not be manifest as sort of

7 an obvious physical disability but will affect

8 all sorts of cognition and learning and

9 et cetera.

10 So all these different -- there are a lot of

11 different acute complications. You can get

12 acute liver problems, you can get a number of

13 problems which require hospitalisation. So

14 that's one aspect of sickle. And during any of

15 those hospitalisations, if you're anaemic or if

16 you -- I should mention the chest crisis where

17 you're sickle in the lungs, and that's -- you

18 get a major respiratory failure.

19 So for a lot of these acute problems you

20 need urgent blood transfusion, which I'll --

21 I can come on to in a bit.

22 So, many sickle patients will have received,

23 at some point in their lives, will have received

24 blood either -- you know, for an emergency

25 indication. That's one side of sickle. Then

<p style="text-align: right;">109</p> <p>1 obviously the other side of sickle is the</p> <p>2 chronic disease, the management. So with many</p> <p>3 years of sickling you can get damage to joints,</p> <p>4 you need joint replacements, you get damage to</p> <p>5 the heart, lungs, liver and kidneys, leading to</p> <p>6 sort of chronic -- chronic organ damage, and all</p> <p>7 these things will contribute to an early</p> <p>8 mortality.</p> <p>9 MS RICHARDS: You've explained in the report that</p> <p>10 transfusion in this context can be used to</p> <p>11 correct anaemia or reduce the proportion of</p> <p>12 circulating sickle cells.</p> <p>13 DR RYAN: Yeah.</p> <p>14 MS RICHARDS: So, as I understand it, transfusion is</p> <p>15 not, in contrast to thalassaemia, the mainstay</p> <p>16 of treatment, but it is, as a practical reality,</p> <p>17 something that many people with sickle cell</p> <p>18 disease will have undergone on more than one</p> <p>19 occasion?</p> <p>20 DR RYAN: Yes.</p> <p>21 MS RICHARDS: Often on repeat occasions?</p> <p>22 DR RYAN: So for some of the complications -- so we</p> <p>23 know from a lot of evidence-based studies that</p> <p>24 it -- if you can predict children who are at</p> <p>25 risk of stroke -- and we can do that now by</p>	<p style="text-align: right;">110</p> <p>1 scanning of the major blood vessels leading to</p> <p>2 the brain, we can actually identify children who</p> <p>3 are likely to or are particularly at risk of</p> <p>4 stroke -- we know that if you give them regular</p> <p>5 blood transfusions you can prevent that stroke</p> <p>6 happening. So that's the standard of care in</p> <p>7 the UK for children. They are screened from</p> <p>8 about the age of two, and if they're at risk</p> <p>9 of -- felt to be at risk of stroke they're</p> <p>10 offered transfusions for a period of time.</p> <p>11 If you've already had a stroke as a child or</p> <p>12 an adult, the evidence shows that transfusion is</p> <p>13 the main treatment to prevent you having</p> <p>14 a further stroke. So that -- those individuals</p> <p>15 tend to stay on long-term transfusion</p> <p>16 programmes. Some patients, you know, have been</p> <p>17 on it for 20 years now.</p> <p>18 The -- we also -- although we have other</p> <p>19 drugs that we can use to try to help prevent the</p> <p>20 painful crisis, some of the chest complications,</p> <p>21 there are number of individuals who have such</p> <p>22 bad disease in terms of coming into hospital for</p> <p>23 pain or other problems, that we offer them</p> <p>24 regular blood transfusions. So, at the moment,</p> <p>25 we probably have -- somewhere between about</p>
<p style="text-align: right;">111</p> <p>1 5-10% of all our SS patients are on regular</p> <p>2 blood transfusions. And by that, typically they</p> <p>3 have a blood transfusion every four to six weeks</p> <p>4 sometimes more often, and we do it in the form</p> <p>5 of exchange blood transfusions. So that's where</p> <p>6 you take out blood and you put donated blood</p> <p>7 back in, and that effectively lowers your sickle</p> <p>8 percentage.</p> <p>9 And that's -- those numbers are increasing</p> <p>10 because our patients are getting older, they're</p> <p>11 getting lung problems, they're getting other</p> <p>12 indications. And actually blood transfusion</p> <p>13 makes them feel -- they don't get pain, you</p> <p>14 know, they're able to go about their normal</p> <p>15 lives, so it really -- I think our threshold for</p> <p>16 giving regular blood transfusions is going down</p> <p>17 all the time.</p> <p>18 MS RICHARDS: In terms of those with sickle cell</p> <p>19 disease, leaving aside for the moment any</p> <p>20 question of hepatitis C, what's the life</p> <p>21 expectancy and how has that changed over the</p> <p>22 years?</p> <p>23 DR RYAN: Well, it's changing all the time. We</p> <p>24 don't really know because actually until</p> <p>25 recently we've not had a significant number of</p>	<p style="text-align: right;">112</p> <p>1 older patients.</p> <p>2 We know -- you can project across a group of</p> <p>3 patients that a study from King's in London</p> <p>4 showed for such patients a life expectancy maybe</p> <p>5 of about in the sixties, but that was a group of</p> <p>6 patients -- and those patients who have the most</p> <p>7 severe disease are typically living into their</p> <p>8 forties still.</p> <p>9 We have introduced new treatments that we</p> <p>10 think will impact on children, and ultimately</p> <p>11 adults, and then we don't know what the impact</p> <p>12 of regular transfusions is. So I -- if you</p> <p>13 asked me to estimate, I would say it's in the</p> <p>14 order of 50s for SS and probably 60s or 70s for</p> <p>15 the other types of sickle.</p> <p>16 So on average, about 20 years, you know,</p> <p>17 less than comparable peers.</p> <p>18 MS RICHARDS: Now, given the amount of blood</p> <p>19 transfusions that many people with sickle cell</p> <p>20 disease may have received, would you agree it</p> <p>21 seems likely that there will have been a number</p> <p>22 of people with sickle cell who received</p> <p>23 transfusions prior to the early nineties who</p> <p>24 would have been infected with hepatitis C as a</p> <p>25 result?</p>

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1 **DR RYAN:** Yes, I would say so. We still have -- we
 2 have -- our patterns in the sickle cell in the
 3 UK reflect periods of immigration. So we still
 4 have a lot of people coming in from Africa and
 5 we still see a lot of hepatitis C acquired in
 6 other parts of the world, but I'm sure --
 7 I think a lot of the patients who had the
 8 chronic hep C prior to the 1990s, I think most
 9 of those would be probably dead by now.
 10 In terms of HIV, I've only seen a couple of
 11 patients with HIV, even in patients who have had
 12 multiple transfusions from east Africa, so I'm
 13 quite sure what the incidence would have been in
 14 HIV, but certainly hepatitis C, I'm sure, yeah.
 15 **MS RICHARDS:** And what would be the additional
 16 affect of hepatitis C upon an individual who has
 17 sickle cell disease?
 18 **DR RYAN:** Well, I think it would probably compound
 19 the risk of developing chronic liver disease.
 20 Now chronic liver disease in sickle again can be
 21 multi-factorial, it can be related to iron
 22 overload from transfusions, it can be related to
 23 sickling, damage to the liver itself, so I think
 24 it would compound the risk of developing chronic
 25 liver disease.

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1 We use transfusion a lot in this country for
 2 medical and surgical problems, when people need
 3 to have blood transfusions either because
 4 they're not making enough blood or they're
 5 losing blood. So this is different from
 6 transfusions that are needed for inherited
 7 conditions that we've been talking about so far.
 8 On the whole, the use of red cells is going
 9 down in the UK. On the whole, the use of
 10 transfusions for surgery is going down in
 11 the UK, as compared to transfusions for medical
 12 conditions, which is going up.
 13 The use of cryoprecipitate is going up in
 14 the UK, and so all of these patterns are
 15 basically reflective of a few advances in
 16 science and practice and policy. So since 2014,
 17 there's been a lot of consciousness about using
 18 blood sensibly, and not overusing blood, and
 19 that's across the world. It's called the
 20 patient blood management philosophy. And that's
 21 been hugely promoted everywhere, including UK.
 22 So the use of blood has fallen as people have
 23 become more conscious that using less blood is
 24 actually okay.
 25 There's been very good quality trials since

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1 I also -- so -- but -- but like
 2 thalassaemia, if patients have got hepatitis,
 3 they are -- they are referred to the -- the
 4 liver teams for managing -- managing it. So --
 5 so it would -- again, anaemia, because they're
 6 baseline, they're quite anaemic, they would
 7 need -- it would compound the anaemia, and they
 8 may need the odd transfusion for that.
 9 **MS RICHARDS:** And as I understand it, there isn't
 10 any data as to the numbers of individuals with
 11 sickle cell disease who might have been infected
 12 through transfusion in the United Kingdom?
 13 **DR RYAN:** No, no. I mean, I was -- I do remember
 14 when we did the look-back exercise in '94,
 15 I worked in hospital with a big sickle
 16 population and we did -- we did encounter
 17 a number of patients who had received blood, but
 18 those patients -- I mean, most of those parents
 19 would not be living now.
 20 **MS RICHARDS:** Can I then ask you to deal with -- or
 21 ask you to deal with the other rare inherited
 22 anaemias and other conditions in which
 23 transfusion would be a significant part or
 24 mainstay of treatment, please.
 25 **DR SEKHAR:** So I'll deal with the latter part first.

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1 the early 2000s to support that. You don't need
 2 as much haemoglobin levels to be present in your
 3 body through a surgical procedure or even in
 4 normal day-to-day life. So previously we would
 5 transfuse people so that the haemoglobin levels
 6 were around 10, 11, or whatever, and these days
 7 we are fairly satisfied with lower levels of
 8 haemoglobin. So these have led to improved use
 9 of red cells.
 10 In conditions where people have severe
 11 bleeding, we also use plasma. So that's FFP.
 12 And we use cryoprecipitate. So these two have
 13 been the mainstream of treatment in inherited
 14 bleeding, historically.
 15 There's still -- plasma is still the
 16 mainstay of inherited Factor V deficiency, but
 17 otherwise we've moved on to more improved
 18 products.
 19 So in people who have severe bleeding, like
 20 trauma or burst blood vessels or cardiac surgery
 21 or liver transplant, it's commonplace to use
 22 a combination of red cells, plasma,
 23 cryoprecipitate and platelets.
 24 In actual fact, when somebody donates a bag
 25 of blood, all of these are included in one bag

<p style="text-align: right;">117</p> <p>1 of blood, but in the UK they are split into 2 separate units, and when people need it they're 3 used in combination of packs. And the number of 4 packs that need to be used over time has changed 5 over time, so we used to use lots of red cells, 6 and quite little of plasma, and there's been 7 lots of very good quality evidence to say that 8 that ratio should reflect real state of blood 9 circulation. So the more blood we use, the more 10 important it is to use a combination of products 11 so that we don't bleed excessively due to lack 12 of plasma. 13 So these have been the sort of patterns of 14 blood use in the UK in the last decade or so. 15 In terms of the outcomes of massive bleeding 16 or major haemorrhages, the improved use and 17 improved availability of blood has made a huge 18 difference to survival, and so lots of 19 statistics have shown that the better quality 20 blood replacement early on in a bleeding 21 patient, the better the outcomes are. And in 22 some sections or in some groups of patients, 23 cryoprecipitate has become a very important part 24 of that treatment. 25 So moving on -- away from patients who</p>	<p style="text-align: right;">118</p> <p>1 bleed, there is the group of patients who might 2 be anticipated to bleed. So there's a diagnosis 3 of, say, bowel cancer and that surgery is likely 4 to lose blood, but you have enough time to make 5 up for the blood while waiting for that 6 operation to happen. 7 So there's lots more emphasis these days on 8 pre-assessment, doing the blood test, treating 9 the anaemia before the surgical procedure is 10 done. So, again, there's been rationalisation 11 of blood use because of improved processes 12 before the operation is done. 13 The second large group of patients who need 14 blood are people whose bone marrow cannot 15 produce blood. And separate from the inherited 16 diseases are conditions like leukaemia where the 17 disease itself interferes with the bone marrow 18 or the treatment interferes with the bone 19 marrow. And such patients are usually dependent 20 on transfusion until the bone marrow can pick 21 up. So that's usually for a period of two or 22 three or four months while they're on incentive 23 treatment. And the kind of transfusion needs 24 for such a patient would be along the lines of 25 two units a week, of red cells, some platelets</p>
<p style="text-align: right;">119</p> <p>1 every so often. And because these are related 2 to the bone marrow, it's not so much affecting 3 of plasma or cryo. 4 So these patients are in need of what we 5 call cellular products, so red blood corpuscles 6 and platelets. 7 Historically, we used to base the amount of 8 red cells and platelets on the figures. So the 9 people will have a blood test every day, know 10 what the platelet counts are, and then we base 11 the transfusion. 12 What's changed in the last 10 years or so is 13 that the thresholds at which we transfuse 14 patients is dropped so it's now considered safe 15 that we don't transfuse at certain level but we 16 transfuse at a much lower level than we used to 17 historically. 18 So again, there's been quite a lot of 19 rationalisation in terms of blood use. And 20 overall, UK adherence to such policies within 21 the groups I'm alluding to is on the whole very 22 good. There's lots been audits undertaken at 23 individual hospitals, across regions, across the 24 country which reflect more or less continuous 25 improvement in how blood is used.</p>	<p style="text-align: right;">120</p> <p>1 In terms of the infectious risk of blood, 2 patients who are identified as needing lots of 3 blood, including patients like sickle cell 4 disease and so on, will be vaccinated for 5 hepatitis B vaccine, and so that's much less 6 a problem. 7 The -- in late -- in 1999 the UK implemented 8 a procedure called leukodepletion which 9 basically removes all the white blood corpuscles 10 from the donated blood at source. Because in 11 England and Wales the National Blood Service is 12 the main provider of blood, this can be done 13 reliably at source. In other countries where 14 you don't have such a centralised system, people 15 would have to buy the filter to be done at the 16 bedside. So it's very variable. 17 But in the UK, it's a very systematic 18 process, and so leukodepletion was done 19 primarily because of the worry about vCJD but 20 has had a lot of benefits in many other ways and 21 has reduced both the reactions related to 22 transfusions but also infection risks related to 23 transfusion. 24 There are a couple of other processes which 25 are available for reducing the infection risk,</p>

<p style="text-align: right;">121</p> <p>1 and they're called pathogen inactivation 2 technologies. Some of them are very old, so for 3 example the solvent detergent plasma that's been 4 available for many, many years is one such 5 technology. But in -- for the cellular products 6 there have been some new technologies, and 7 across the world they're variably implemented. 8 The commonest technology is to make platelets 9 safer, and the main worry with platelets is more 10 about bacterial infection rather than viral 11 infection.</p> <p>12 So pathogen inactivation of platelets is 13 practised in different countries like 14 Switzerland, Kazakhstan, et cetera, but in this 15 country it was assessed by the SaBTO working 16 group. The existing practice for platelets was 17 thought to be so robust that we don't really 18 need that at the present time.</p> <p>19 The red cell safety pathogen inactivation is 20 work in progress, and there's a very good trial 21 that was done in Ghana, along with 22 Professor Aline from Cambridge, who -- and that 23 trial established that malaria risk was much 24 reduced by pathogen inactivating. In this 25 country it's still on a trial basis because,</p>	<p style="text-align: right;">122</p> <p>1 again, our products are deemed sufficiently 2 safe.</p> <p>3 In terms of inherited --</p> <p>4 DR RYAN: For -- the inherited anaemias tend to be 5 managed by the same doctors that manage 6 thalassaemia, because they are conditions where 7 you either don't produce enough red blood cells 8 or you have an abnormal haemoglobin or have 9 a haemolytic anaemia where the red cells are 10 broken down. So they're managed in much the 11 same way with transfusions, as required for 12 symptoms or specific complications, and they 13 have a tendency to load with iron as well.</p> <p>14 It should be mentioned that even if you 15 don't have transfusions or you have very 16 infrequent transfusions with both thalassaemias 17 and some of these disorders you can still 18 accumulate significant amounts of iron, because 19 of the way the body reutilises the iron, and 20 still need to take iron chelation drugs.</p> <p>21 MS RICHARDS: I'm going to move on next to the 22 primary immunodeficiency disorders, and ask 23 Professor Edgar and Dr Marshall to address that. 24 Could you tell us again -- perhaps 25 crystallise with some quite complicated science</p>
<p style="text-align: right;">123</p> <p>1 and some names that are definitely beyond my 2 skills of pronunciation, and tell us a little 3 bit about PIDs.</p> <p>4 PROFESSOR EDGAR: Okay, so primary 5 immunodeficiencies are a group of conditions 6 where one or other or indeed several components 7 of the immune system aren't working properly, 8 and that renders effective people vulnerable to 9 infections.</p> <p>10 The first primary immune deficiencies were 11 described in the 1950s, and the number of these 12 conditions has increased exponentially over that 13 time. There are now probably 400 different 14 conditions. And they affect all age ranges, 15 from newborn infants to people in their older 16 age groups.</p> <p>17 There's a range of severities. So at the 18 most severe end of the spectrum is a condition 19 called severe combined immune deficiency, where 20 multiple components of the immune system are 21 defective, and that usually presents in the 22 early months of life, and such babies would 23 require bone marrow -- stem cell 24 transplantation.</p> <p>25 At the more mild end of the spectrum, some</p>	<p style="text-align: right;">124</p> <p>1 people will have an isolated deficiency of an 2 immunoglobulin or antibody molecule which might 3 not even need treatment. But then there's 4 a group of what are called primary antibody 5 deficiencies, which are the -- probably the main 6 group in most of our practices in Europe and the 7 UK, where patients don't make immunoglobulins or 8 antibody molecules effectively, and as a result 9 they're vulnerable particularly to recurrent 10 infections, particularly chest disease, and one 11 of the mainstays of treatment for that group of 12 patients is immunoglobulin replacement, and 13 that's obviously a blood-derived pharmaceutical 14 product.</p> <p>15 In terms of numbers of affected people, we 16 have a UK national registry, we have European 17 registries, and at present, there are 18 about 5,000 people in the UK registered as 19 having a primary immune deficiency, although we 20 know the actual number is probably closer to 21 twice that amount. That's because there's 22 incomplete registration of these patient 23 numbers.</p> <p>24 And as I say, the most common group of these 25 disorders in the UK would be the primary</p>

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1 antibody deficiencies.

2 **MS RICHARDS:** And as you say, the long-term

3 treatment with blood products has been

4 a cornerstone of treatment for some types of

5 these primary immuno-deficiencies for a number

6 of decades.

7 **PROFESSOR EDGAR:** That's correct. Really

8 immunoglobulin replacement therapy was commenced

9 when the first case was reported in the 1950s,

10 of a young boy who had what was called

11 Exlingpayglob(?) anaemia.

12 The availability of that treatment has

13 developed over the years. In the 1970s and

14 '80s, immunoglobulin was given by intra-muscular

15 injection, which was a very painful process, and

16 which resulted in partial correction of

17 immunoglobulin levels. Because of technological

18 advances then in the 1980s and '90s, intravenous

19 immunoglobulin replacement therapy became

20 available, and that was given by infusion

21 routinely once every three weeks or so for most

22 patients.

23 Since then there have been developments in

24 terms of giving immunoglobulin by

25 self-administration, usually subcutaneously.

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1 immunoglobulin replacement therapy is a human

2 blood product which consists of immunoglobulin

3 extracted from donated plasma which has been

4 separated from units of blood from thousands of

5 blood donors.

6 **PROFESSOR EDGAR:** Yes, that is correct.

7 **MS RICHARDS:** And it was first used in the treatment

8 of patients with a primary antibody deficiency

9 in 1952 and in the UK since 1956?

10 **DR MARSHALL:** Yes.

11 **PROFESSOR EDGAR:** Yes.

12 **MS RICHARDS:** And you've observed in your report

13 this: you say this:

14 "It's always been recognised that there is

15 a risk of the transmission of plasma-borne

16 infectious agents from immunoglobulin

17 replacement therapy. In the review article

18 published in 1957, the panel suggested that no

19 fraction prepared from pooled plasma by any

20 technique be presumed to be free from the virus

21 of homologous serum hepatitis unless shown to be

22 so by volunteer studies or by application of

23 effective sterilising technique."

24 One of the questions I've been asked to ask

25 by core participants is just to define what that

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1 That's not an injection to the vein but under

2 the skin, usually of the tummy or the thigh, and

3 that can be done by patients independently at

4 home, possibly once a week, that sort of

5 frequency. Those are the main modalities of

6 treatment now.

7 **DR MARSHALL:** If I might add, it's worth noting that

8 immunoglobulin is actually widely used now for

9 non-primary immune deficiency conditions. For

10 a number of secondary immune deficiencies which

11 are caused by other problems, such as blood --

12 or other blood disorders or cancer, but also for

13 neurological conditions, where very high doses

14 of immunoglobulin can be used to prevent

15 inflammation. So the distribution of usage of

16 immunoglobulin now compared to the eighties and

17 nineties is very different, but we've

18 concentrated on the primary antibody

19 deficiencies in all this discussion because that

20 was the group that was treated at the time that

21 this Inquiry is interested in.

22 **PROFESSOR EDGAR:** The group that Sara refers to, the

23 secondary antibody deficiencies, that's the

24 fastest area of increase in immunoglobulin use.

25 **MS RICHARDS:** I think you said in your report that

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1 term is, homologous serum hepatitis.

2 **DR MARSHALL:** That was a term that was used back in

3 the 1950s, and that was just a generic term for

4 serum -- for what we would now call

5 a blood-borne hepatitis, but that just reflects

6 the changes in vocabulary over the time.

7 **MS RICHARDS:** You've identified three known

8 outbreaks of hepatitis C infection related to

9 immunoglobulin usage in the United Kingdom.

10 Could you just talk us through those?

11 **DR MARSHALL:** Yes, there were a number of -- when

12 intravenous immunoglobulin was -- started to be

13 used, which is in the 1980s, it was noted that

14 there were small groups of patients who

15 presented with either -- acute hepatitis, which

16 could either be attributed to hepatitis B or to

17 what was then called non-A/non-B hepatitis. The

18 largest group was the last one, in 1994, where

19 a cohort of patients, I think it's 36 patients

20 in the UK, but as part of a much larger group of

21 patients in the US, presented with acute

22 hepatitis in the weeks after having a very

23 specific batch of immunoglobulin.

24 We know quite a lot about that episode

25 because it was very -- studied in great deal at

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1 the time. And what we know is that because of
 2 the way the patients were being monitored -- at
 3 that time in the UK it was standard to have
 4 liver function tests every six weeks, and we
 5 know that patients presented with -- there were
 6 three patients who presented with a blip,
 7 a slight increase in their liver function tests
 8 within weeks of getting this particular batch.
 9 What that led the doctors at the time to do
 10 was a look-back to see what these patients had
 11 in common, and it was identified that they had
 12 all received immunoglobulin from a specific
 13 manufacturer, and that they all then -- when
 14 they went back in more detail, they could see
 15 that it came from a specific batch.
 16 So that was a very defined episode. They
 17 were all -- all the affected patients were then
 18 shown to have the same hepatitis genotype, so it
 19 was all tracked back. And that's been the
 20 biggest episode that's been described, and we've
 21 learnt quite a lot about hepatitis C in this
 22 group through the study of that group of
 23 patients.
 24 **MS RICHARDS:** And you've said in the report in
 25 relation to that 1994 outbreak, 29 of the

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1 you described in your report, one was in 1983.
 2 **DR MARSHALL:** Yes.
 3 **MS RICHARDS:** And you've said a British-produced
 4 plasma product was implicated, and then the
 5 second occurred in relation to Scottish product
 6 in Scottish patients.
 7 **DR MARSHALL:** That's correct.
 8 **MS RICHARDS:** Do you remember the date of that
 9 second one?
 10 **DR MARSHALL:** I can give it to you but it's not on
 11 the top of my head.
 12 **MS RICHARDS:** Thank you. Because the report doesn't
 13 say.
 14 **DR MARSHALL:** No.
 15 **MS RICHARDS:** We have a footnote which gives us the
 16 date of a paper which may -- (overspeaking)
 17 **DR MARSHALL:** No, I can give you that.
 18 **MS RICHARDS:** And do you know, again, off the top of
 19 your head -- don't worry if you don't -- the
 20 numbers, other than it was less than --
 21 **DR MARSHALL:** Small. Well, it was a small --
 22 I think it was less than ten in each case.
 23 **MS RICHARDS:** And has there been any long-term
 24 follow-up that you're aware of in relation to
 25 either of those two cohorts?

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1 patients who received this particular product
 2 from Baxter Pharmaceutical were found to be
 3 hepatitis C positive on two or more occasions.
 4 **DR MARSHALL:** That's correct. And they have
 5 subsequently been -- they have been followed
 6 up -- shall I talk a little bit about the
 7 natural history of --
 8 **MS RICHARDS:** Yes, please.
 9 **DR MARSHALL:** So in the UK only, there were 36,
 10 I think, patients identified as being exposed,
 11 of whom 29 had a positive test on more than two
 12 occasions. When they look at that cohort of
 13 patients five years later, they found that 25%
 14 of the patients had either got end-stage liver
 15 disease or had died with associated liver
 16 disease. So much more rapid progression of
 17 disease than would be expected in a group of
 18 patients with a normal immune system.
 19 I think that people had always recognised
 20 that this group of patients was particularly
 21 susceptible because their immune system doesn't
 22 work very well. But this kind of gave us
 23 a measure of just how aggressive hepatitis C
 24 could be in this group.
 25 **MS RICHARDS:** Just the two earlier outbreaks that

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1 **DR MARSHALL:** There has been no systematic follow-up
 2 of those two cohorts. Partly because at the
 3 time, it was very difficult to identify the
 4 non-A non-B, it was hard to see them as a cohort
 5 because there wasn't the same discipline --
 6 sorry?
 7 **PROFESSOR EDGAR:** And the testing wasn't available.
 8 **DR MARSHALL:** And the testing wasn't available.
 9 **MS RICHARDS:** And this was at some point in the 80s?
 10 **DR MARSHALL:** Yes.
 11 **MS RICHARDS:** What's then -- are there any
 12 differences in terms of either natural history
 13 diagnosis and treatment of hepatitis in
 14 individuals with primary immune deficiencies?
 15 **DR MARSHALL:** Yes. I mean in terms of the natural
 16 history, I've already alluded to the fact that
 17 this group of patients has particularly
 18 aggressive disease, presents much earlier than
 19 we would expect. More people develop more
 20 severe disease more quickly, to answer that
 21 first question about natural history.
 22 In terms of diagnosis, because these
 23 patients don't make antibody, that's why they're
 24 having the immunoglobulin, all the standard
 25 antibody-based tests that we would do in

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1 patients with a normal immune system don't work.
 2 And so the normal immuno assays that we were
 3 talking about before, or on Wednesday, are not
 4 applicable in this patient group, and that means
 5 that in those early episodes one might miss --
 6 one might get a falsely negative result because
 7 you were using the wrong tests.
 8 Once viral load and the PCR-based tests came
 9 in, those were the tests that can be used in
 10 this patient group, and those are the tests that
 11 we continue to use in this patient group. So
 12 there is a difference in diagnosis.
 13 In terms of treatment, the patients affected
 14 in the 1993/4 episode, some of them received
 15 interferon, and some of them subsequently
 16 received interferon ribavirin.
 17 Not enough to be able to give a definitive
 18 "they do better" or "they do worse", but we do
 19 know that in terms of transplantation this is
 20 a patient group who often have other infectious
 21 complications because of the nature of their
 22 problem.
 23 And if you have a chronic infection of any
 24 type and undergo a transplant, you're much more
 25 likely that that infection will get worse and

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1 immunoglobulin does not appear to transmit
 2 hepatitis C. In contrast, intravenous
 3 immunoglobulin has been shown to. Subcutaneous
 4 immunoglobulin, which David referred to earlier,
 5 which is a often-used form of immunoglobulin
 6 now, has not been shown to transmit it but may
 7 do.
 8 Quite why immunoglobulin intramuscular
 9 immunoglobulin doesn't and intravenous
 10 immunoglobulin does is not completely clear. It
 11 may be because the preparations are different,
 12 it may be other subtle differences in the way
 13 the immune system that is there responds to
 14 clearing the virus.
 15 **MS RICHARDS:** And as I understand it, the reason why
 16 intramuscular immunoglobulin is no longer the
 17 favoured method of treatment is not because of
 18 issues in relation to transmission of hepatitis.
 19 **DR MARSHALL:** No.
 20 **MS RICHARDS:** But because it's -- as you were
 21 describing, Professor, it's a more painful and
 22 problematic --
 23 **PROFESSOR EDGAR:** And less effective. You don't
 24 achieve the same sort of plasma levels that you
 25 want to.

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1 that may be life threatening.
 2 So the opportunity for transplantation is
 3 not always available for this patient group.
 4 **MS RICHARDS:** And then were you able to find any
 5 reference to HIV being transmitted to this
 6 particular category of patients --
 7 **DR MARSHALL:** That's a very good question, and in
 8 fact there are no reported cases of HIV
 9 associated with immunoglobulin contamination in
 10 the literature. And the reason for that is
 11 probably because HIV is a retrovirus, it's
 12 a different kind of virus to hepatitis C, and it
 13 appears that the manufacturing process, the
 14 standard first step of the manufacturing process
 15 in the preparation of immunoglobulin destroys
 16 the wall of the HIV, and so in fact kills the
 17 virus.
 18 **MS RICHARDS:** There are two methods you described of
 19 immunoglobulin being administered,
 20 intra-muscular and intravenous, and I understand
 21 there's a difference in terms of infection with
 22 hepatitis through those two routes.
 23 **DR MARSHALL:** Yeah, which is very interesting.
 24 Intramuscular immunoglobulin was standard
 25 practice until the 1980s, and intramuscular

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1 **MS RICHARDS:** Can you assist with this: what, if
 2 any, steps are you aware of that were put in
 3 place to try to identify patients affected by
 4 viral contaminated immunoglobulin?
 5 **DR MARSHALL:** Well, I think I might answer that
 6 question by describing the steps that were put
 7 in place to -- rather than doing the look-back,
 8 but in -- prospectively. When patients are
 9 started on immunoglobulin -- I'll describe what
 10 happens now and then go back.
 11 When patients are started on immunoglobulin
 12 now, first of all one would take their consent
 13 and advise patients about the risks of -- the
 14 theoretical risk of HIV, of hepatitis B,
 15 hepatitis C, variant CJD, and also unknown
 16 viruses that we -- and other infectious agents
 17 that we don't know about.
 18 We would always screen patients for whether
 19 or not they had hepatitis or HIV before giving
 20 them treatment. And we would then -- and test
 21 their liver function test as a routine.
 22 Patients then undergo regular testing for their
 23 liver function every three months, once they
 24 start on treatment. And then, once a year, they
 25 would, in most centres, or many centres, would

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1 have blood stored, so that if problems arise in
 2 the future, one can then look back and get an
 3 idea of when they may have been infected.
 4 Now those -- there are a few other steps
 5 that were taken. One is to restrict the
 6 product -- there are a number of different
 7 immunoglobulin products available, and patients,
 8 once they were stable on one product, would stay
 9 on that product rather than mix and match with
 10 many different products. And the idea behind
 11 that was to minimise the risk: if you're only
 12 having one product, and preferably only having
 13 a limited number of batches of that product,
 14 your risk is limited.
 15 Those steps were put in place in around
 16 the 1990s. There was a document, which was
 17 called the Consensus Document on the Diagnosis
 18 and Treatment of Primary Antibody Deficiencies,
 19 which was a very influential document, and this
 20 laid out exactly what the standard of care was.
 21 And in the UK, most of the centres really
 22 adhered to that, and these steps were all laid
 23 out in that document.
 24 **MS RICHARDS:** And that was 1994?
 25 **DR MARSHALL:** That was 1994. 1994/5.

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1 outbreaks or episodes, as far as you and your
 2 colleagues are aware, since 1994, patients will
 3 nonetheless be advised, as part of the obtaining
 4 of consent process, about the risk of viral
 5 contamination?
 6 **DR MARSHALL:** Yes, yes.
 7 **MS RICHARDS:** Including hepatitis B, C?
 8 **DR MARSHALL:** Yes.
 9 **MS RICHARDS:** Including HIV?
 10 **DR MARSHALL:** Yes.
 11 **PROFESSOR EDGAR:** Yes.
 12 **MS RICHARDS:** What about the possible exposure to
 13 vCJD?
 14 **PROFESSOR EDGAR:** Yes.
 15 **DR MARSHALL:** Yes.
 16 **MS RICHARDS:** So that's all part of it --
 17 **DR MARSHALL:** So there are five -- there are the
 18 five, which is HIV, hepatitis B, hepatitis C --
 19 and now I'm going to forget them -- variant CJD,
 20 and the unknowns.
 21 **PROFESSOR EDGAR:** And the unknowns, yes.
 22 **MS RICHARDS:** So they're told that.
 23 **PROFESSOR EDGAR:** Yes.
 24 **MS RICHARDS:** Will the nature of those risks
 25 typically be discussed with them?

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1 **MS RICHARDS:** You say in your report that since the
 2 1994 outbreak that you've described, there has
 3 not, as far as it's known, been any further
 4 immunoglobulin-associated viral contamination.
 5 **DR MARSHALL:** In the UK.
 6 **MS RICHARDS:** In the UK.
 7 **PROFESSOR EDGAR:** Yes.
 8 **DR MARSHALL:** Correct.
 9 **MS RICHARDS:** And that, as I understand, has led to
 10 some ongoing discussions about whether you still
 11 need to keep samples frozen and whether you
 12 still need to have annual screening.
 13 **PROFESSOR EDGAR:** That's correct, yes. I mean, the
 14 steps that Sara has described are widely
 15 practised but there is now a bit of a debate as
 16 to whether we really need to do all of them
 17 because the improvements in product
 18 manufacturing processes and the length of time
 19 since there's ever been a problem is leading
 20 people to kind of challenge that a little bit.
 21 **MS RICHARDS:** And then can I just go back to
 22 something you said a few moments ago,
 23 Dr Marshall, which was about the consent
 24 process.
 25 Notwithstanding the lack of any further

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1 **PROFESSOR EDGAR:** Yes. I mean, typically people
 2 will be told that there is a risk of getting
 3 these viral infections, that these infections
 4 can be very severe, but that will be tempered --
 5 I mean, in this day and age -- you know, in --
 6 at this time we would be saying: it has been
 7 a long time, 25 years, since anyone has ever got
 8 it through this route.
 9 But there are a lot of unknowns,
 10 particularly around variant CJD and the viruses
 11 we don't know about. And so that would be
 12 alluded to. And patients are usually given
 13 information sheets so they can take them home
 14 and read them again, because the context of
 15 a clinic space is not always the best place.
 16 So we do always give written material as
 17 well, that says that.
 18 **MS RICHARDS:** And would the standard practice be to
 19 obtain written consent before undergoing
 20 immunoglobulin treatment?
 21 **DR MARSHALL:** Yes.
 22 **PROFESSOR EDGAR:** Yes.
 23 It's possibly also worthwhile commenting
 24 that this doesn't all happen in one
 25 consultation, because usually when you're seeing

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

19 **MS RICHARDS:** Then last question before the break,
 20 sir.
 21 Do you think that there may be undiagnosed
 22 patients, so patients with primary
 23 immunodeficiency disorders who received
 24 immunoglobulin replacement therapy in the
 25 periods with which we're talking about who may

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

6 **MS RICHARDS:** And it's an issue to which the Inquiry
 7 will undoubtedly be returning in the future,
 8 I've no doubt on more than one occasion.
 9 Sir, that completes my questions but I'm
 10 conscious core participants may well have
 11 questions they want me to ask the panel, so this
 12 may well be the ideal moment.

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

20 **MS RICHARDS:** Very happy with that, sir.
 21 **SIR BRIAN LANGSTAFF:** So let's take ten minutes now
 22 and there will be coffee or tea available when
 23 we finish, which won't be long after that.

24 **(3.04 pm)**
 25 **(A short break)**

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

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

20 **PROFESSOR EDGAR:** Yes, I would agree.
 21 **MS RICHARDS:** And that --
 22 **DR SEKHAR:** It is worth perhaps commenting about the
 23 last aspect of the conversation here, which
 24 is -- so this -- this question of informing
 25 people about the risks of any blood product is

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1 **(3.19 pm)**
 2 **MS RICHARDS:** Sir, there are a handful of questions
 3 that core participants have asked me to ask.
 4 They're primarily, I think, going to be relevant
 5 to Dr Tunstall and Dr Gooding's areas of
 6 expertise because they're in the context of
 7 bleeding disorders for most part.
 8 The first is, in relation to gene therapy we
 9 talked about current treatments and developments
 10 but in fact I didn't ask you about gene therapy
 11 and what might be happening in that regard.
 12 Are you able to assist?

13 **DR TUNSTALL:** Certainly.
 14 So gene therapy is an area of very active
 15 research in haemophilia at the moment, and there
 16 have been some very encouraging studies in both
 17 haemophilia and haemophilia -- haemophilia A and
 18 haemophilia B, with stable levels, or -- or
 19 stable-ish levels of expression which are coming
 20 out for some years.
 21 We haven't yet seen a movement into
 22 a commercial market, it's certainly in the place
 23 of research projects at present. And we don't
 24 know if that response will be sustained
 25 indefinitely or whether it will be something

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1 that will be there for a number of years and
 2 then wane from there.
 3 So it's certainly something on the horizon.
 4 How swiftly it moves from being on the horizon
 5 to everyday practice, I don't think we know yet.
 6 There were particular barriers for children
 7 with the current technologies in that it
 8 wouldn't be predicted to work in children due to
 9 liver cell turnover, at present.
 10 **MS RICHARDS:** And the aim of the gene therapy that's
 11 the subject of the research you refer to is to
 12 have higher lifelong levels of factor? Is that
 13 right?
 14 **DR TUNSTALL:** I guess potentially lifelong, although
 15 whether, you know -- a decade or more might be
 16 something to look at, yeah.
 17 **DR RYAN:** Can I add that gene therapy looks very
 18 promising for thalassaemia, and in fact NICE are
 19 considering the use of commissioning of gene
 20 therapy in a few months' time for certain groups
 21 patients, and the data suggests that gene
 22 therapy gives the vast majority of patients --
 23 they become transfusion independent. So it's
 24 actually a very promising treatment for
 25 thalassaemia, and it's under trial for sickle,

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1 not sure whether you would be able to answer
 2 this but I'm going to ask you and see. So
 3 it's -- the position of people with haemophilia
 4 infected with HIV and/or hepatitis C, are there
 5 any concerns that anti-depressants have had any
 6 particular detrimental effect or created side
 7 effects for that cohort?
 8 **DR GOODING:** In theory there is a potential acquired
 9 platelet dysfunction sort of element to some
 10 anti-depressants, but whether it's a significant
 11 affect in terms of haemophilia outcome, I'm not
 12 sure. I know I would say that it's not
 13 something that we would -- I think the -- the
 14 caveat with prescribing anti-depressants for
 15 people with bleeding disorders is that they
 16 would be used with caution, and typically
 17 I think if -- if you were to see a side effect
 18 like that, you'd -- you would pick up on it
 19 fairly quickly. It tends to manifest itself
 20 with easy bruisability.
 21 **DR TUNSTALL:** Is that a question specifically about
 22 antiviral drugs?
 23 **MS RICHARDS:** I'm afraid I don't know. The question
 24 is the question I read out.
 25 **DR TUNSTALL:** So I would agree with Richard about

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1 where, again, it looks very promising as well.
 2 **MS RICHARDS:** The next question again relating to
 3 the treatment for bleeding disorders. Is it
 4 correct that very recently, so this month,
 5 a decision has been made, at least in relation
 6 to England, not to fund recombinant treatment
 7 for VWD and Factor VIII deficiency?
 8 **DR TUNSTALL:** I'm not aware what is in the public
 9 domain or not, for that.
 10 **MS RICHARDS:** Well, it's sufficiently in the public
 11 domain that somebody has given it to me as
 12 a question to ask.
 13 I am told, and I have no knowledge myself of
 14 this, that NHS England has made a decision not
 15 to fund recombinant treatment for people with
 16 VWD or Factor VIII deficiency.
 17 **DR TUNSTALL:** I believe that the case, yes.
 18 **MS RICHARDS:** So that will leave those particular
 19 deficiencies reliant in part upon plasma-based
 20 treatment, although there's obviously also in
 21 relation to VWD -- DDAVP, as we've already
 22 discussed?
 23 **DR TUNSTALL:** Yes.
 24 **DR GOODING:** Yes.
 25 **MS RICHARDS:** Then the -- there's a question, I'm

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1 that aspect but I don't know about the question
 2 with -- specifically.
 3 **MS RICHARDS:** The next question I'm asked to ask you
 4 is about the assays, so going back to the
 5 question of diagnosis, when it's appropriate to
 6 use stage 1 assay and when stage 2 assay?
 7 **DR TUNSTALL:** So from -- there's basically two
 8 different ways of doing a Factor VIII assay, and
 9 they usually give a very consistent results.
 10 There is sometimes a discrepancy with certain
 11 abnormalities in the Factor VIII gene that there
 12 is a discrepancy. It's not usually a case of
 13 being entirely normal on one case and -- and it
 14 showing, say, severe haemophilia the other way.
 15 It's usually the baseline level changes, or what
 16 we would consider the functional level. So it
 17 is our practice -- we consider it best practice
 18 for anyone with a diagnosis of haemophilia to do
 19 a two-stage or chromogenic assay.
 20 There are also situations where, for
 21 monitoring therapy, a chromogenic or two-stage
 22 assay is more appropriate.
 23 **MS RICHARDS:** Again, I'm afraid with the two of you,
 24 how does the severity of a person's haemophilia
 25 affect the advice you would give them about the

<p style="text-align: right;">149</p> <p>1 activities they should avoid?</p> <p>2 DR GOODING: I suppose it depends on their -- it's</p> <p>3 a very individualised sort of decision, that,</p> <p>4 I think. You may advise people with a bit of --</p> <p>5 a more severe condition that they can</p> <p>6 participate in certain activities when they feel</p> <p>7 that their treatments -- say they're on</p> <p>8 prophylaxis, that would render them safer</p> <p>9 perhaps, than perhaps someone who is a more</p> <p>10 severe-moderate sort of -- I was going to say,</p> <p>11 it needs to be very carefully tailored to -- to</p> <p>12 the patient and what you think their risk is,</p> <p>13 and -- and also their bleeding phenotype, so not</p> <p>14 just the -- the numerical levels but actually</p> <p>15 how they are themselves. And then the advice</p> <p>16 then is -- is a negotiation, I suppose, about</p> <p>17 risk. And I think this -- it's all about trying</p> <p>18 to present information to a patient and their</p> <p>19 family about, you know, how much they want to do</p> <p>20 something and what the risks of that might be</p> <p>21 and whether they're happy to accept those risks</p> <p>22 and if there is anything we can do to modify</p> <p>23 those risks to enable people.</p> <p>24 So that's the sort of context, I think, of</p> <p>25 that sort of advice. It's not as simple as, you</p>	<p style="text-align: right;">150</p> <p>1 know, just numbers.</p> <p>2 MS RICHARDS: Then there's a specific haemophilia B</p> <p>3 related question, what is leiden haemophilia B,</p> <p>4 and what treatment would sufferers be expected</p> <p>5 to receive, and why?</p> <p>6 DR TUNSTALL: So that's -- I mean, it's one case</p> <p>7 where we really do see dramatic differences in</p> <p>8 -- in factor levels, with factor B leiden, and</p> <p>9 we would often see a normalisation or much</p> <p>10 higher Factor IX levels post-puberty, and so</p> <p>11 sometimes it's to the extent that you will</p> <p>12 have -- you see boys with moderate haemophilia B</p> <p>13 who -- who may be severely enough affected to</p> <p>14 require prophylaxis but then the levels rise</p> <p>15 with puberty and they may never need to</p> <p>16 administer treatment again.</p> <p>17 MS RICHARDS: In severe haemophilia what's the</p> <p>18 average Factor VIII level you would aim to</p> <p>19 achieve? So in severe haemophilia A? Is there</p> <p>20 an average Factor VIII level you aim to achieve?</p> <p>21 DR TUNSTALL: It depends on the context, and when</p> <p>22 we're saying -- if we're talking about</p> <p>23 prophylaxis or if we're talking -- covering for</p> <p>24 surgery, so -- so these, or -- or after a bleed,</p> <p>25 and all of these things will be different</p>
<p style="text-align: right;">151</p> <p>1 situations, if we're talking about prophylaxis,</p> <p>2 we generally don't aim so much on peaks and more</p> <p>3 on the troughs. So we try to preserve a level.</p> <p>4 I think most of us are unhappy with a trough</p> <p>5 that is less than 1 and much happier if the</p> <p>6 trough is above 3. We may, you know, personally</p> <p>7 be happier if the trough is 10, but there's</p> <p>8 limitations of cost and technologies in</p> <p>9 achieving that.</p> <p>10 We don't really know about peaks and</p> <p>11 prophylaxis, how important they are. So it's</p> <p>12 less about aiming for a peak and more about</p> <p>13 sustaining a process level.</p> <p>14 DR GOODING: And, again, having a clinical response</p> <p>15 to the number of bleeds that you're seeing and</p> <p>16 the symptomatic joint problems at the same time.</p> <p>17 MS RICHARDS: And on the topic of prophylactic</p> <p>18 treatment, is the aim to preserve joints or</p> <p>19 prevent joint damage, preserve life, or both?</p> <p>20 DR TUNSTALL: Preserve life as in prevent death</p> <p>21 or --</p> <p>22 MS RICHARDS: I'm assuming that's -- I think that's</p> <p>23 what lies behind the question, yes.</p> <p>24 DR TUNSTALL: I mean, obviously, both. But we know,</p> <p>25 you know, if we have adequate levels to prevent</p>	<p style="text-align: right;">152</p> <p>1 joint damage, then that's going to dramatically</p> <p>2 reduce the risk of life-threatening bleeding.</p> <p>3 MS RICHARDS: Then two slightly broader questions.</p> <p>4 Again it may be that the panel's able to answer</p> <p>5 them or not, or that we need to direct them</p> <p>6 elsewhere. The first is, does hepatitis</p> <p>7 infection cause immunodeficiency?</p> <p>8 PROFESSOR EDGAR: It doesn't cause primary</p> <p>9 immunodeficiency, but chronic illness can, by</p> <p>10 its nature, cause a degree of immunodeficiency.</p> <p>11 Would you agree with that?</p> <p>12 DR MARSHALL: I'd agree with that.</p> <p>13 MS RICHARDS: Very final question, what pathogens</p> <p>14 are thought to be transmitted through blood</p> <p>15 products in the United Kingdom now?</p> <p>16 And if you don't feel able to answer that,</p> <p>17 that's fine, but if you do, please do.</p> <p>18 DR SEKHAR: We usually counsel for the five that</p> <p>19 Sara eluded to, but every so often the Blood</p> <p>20 Service will screen for lots of contemporary</p> <p>21 ones, so that list changes from time to time.</p> <p>22 MS RICHARDS: Okay. Thank you. Those are the</p> <p>23 questions. I'm just going to turn my back to</p> <p>24 see if there is anything vital and pressing?</p> <p>25 No, I'm happy to say not.</p>

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1 **SIR BRIAN LANGSTAFF:** Well, that was indeed the last
 2 question because I have none of my own.
 3 It just remains for me to thank you hugely
 4 for coming to give your time and your evidence
 5 to us. It may have seemed to each pair of you
 6 that there have been a form of selective silence
 7 at times because of the way in which you have
 8 your own particular specialties, but I hope you
 9 see how they all fit together and how it was
 10 useful for us to present you as a panel dealing
 11 with the different conditions that you've dealt
 12 with and informed us about so beautifully.
 13 So thank you very much.
 14 [Applause]
 15 Now you have something to deal with,
 16 I think, but it doesn't require our experts to
 17 stay.
 18 You're very welcome to stay where you are,
 19 perfectly happy, but you may prefer to sit
 20 elsewhere, you may prefer to go. It's entirely
 21 up to you.
 22 Ms Richards?
 23 **MS RICHARDS:** Yes, sir. So I mentioned on Monday
 24 that we had directed some questions to those
 25 responsible for decisions about NHS services in

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1 responses were from the four parts of the UK,
 2 because we know the from the individual evidence
 3 we've heard that, on the ground, people have not
 4 had necessarily a consistent answer from their
 5 own treating hospitals and trusts.
 6 So the response in relation to Scotland --
 7 we had several witness statements from Scotland.
 8 These will be published on the Inquiry website
 9 hopefully later today if not earlier next week.
 10 On this particular issue, in fact, the
 11 Scottish Government asked Professor Dillon, whom
 12 you heard from as part of the evidence this
 13 week, to provide a response, and the response
 14 was this. So in response to the question about
 15 scans, blood tests and other checks, he said
 16 this:
 17 "These have changed and continued to change
 18 radically and are continually updated in
 19 national and international guidelines as new
 20 evidence emerges. In summary, a person
 21 diagnosed with hepatitis C should have either
 22 bloods, liver function tests and full blood
 23 count, to calculate an FIB4 score or other
 24 estimate of fibrosis or an imaging-based
 25 estimate, eg fibroscan, to stage their disease.

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1 the four parts of the United Kingdom. And I'm
 2 just going to summarise and read shortly from
 3 some of the responses that were received.
 4 So we asked a slightly wider range of
 5 questions than I'm going deal with now.
 6 The first category of questions I'm going to
 7 deal with are about hepatitis C, and we asked
 8 two questions that I'm going to describe:
 9 What scans, blood tests and/or other checks
 10 and/or monitoring are or should be offered to
 11 a person who's been diagnosed with hepatitis C?
 12 How often, and over what period of time is the
 13 first question asked.
 14 And the second:
 15 Following successful treatment such that the
 16 person has received a sustained virological
 17 response, what follow-up scans, blood tests
 18 and/or other checks or monitoring are or should
 19 be offered, how often, and over what period of
 20 time?
 21 So we asked about the current clinical
 22 practice or what should be the current clinical
 23 practice and availability of care in that
 24 regard.
 25 I'm just going to read briefly what the four

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1 Those who don't have evidence of cirrhosis may
 2 be treated and a blood test obtained at 12 or 24
 3 weeks post treatment to confirm success and then
 4 discharged. Those with evidence of cirrhosis
 5 should be treated and remain under six-monthly
 6 review to screen for complication of cirrhosis,
 7 in particular hepatocellular carcinoma with
 8 six-monthly hepatic ultrasounds and estimations
 9 of alpha-theta protein and gastrointestinal
 10 varices, three-yearly upper gastrointestinal
 11 endoscopy."
 12 Then in response to the question about
 13 context and monitoring following SVR,
 14 effectively already answered, but he said this:
 15 "Again, this area has changed considerably
 16 due to the development of the evidence base,
 17 especially around the confidence that SVR is
 18 a marker of HCV cure, thus the need for long
 19 term follow-up has been removed for most
 20 patients. As described above, follow up depends
 21 on the degree of liver damage, those with
 22 cirrhosis needing follow-up."
 23 Of course, we had a slight amplification of
 24 that in the course of his evidence this week.
 25 The position in relation to Wales is set out

<p style="text-align: right;">157</p> <p>1 in a statement from Professor Chris Jones, the 2 Deputy Chief Medical Officer, and he said this: 3 "It depends somewhat on the patient's 4 circumstances and choice. In general, where 5 possible the following pathway is followed. 6 Baseline blood tests including urea and 7 electrolytes, liver function tests, estimated 8 glomerular filtration rate, international 9 normalised ration, full blood count, viral load, 10 genotype and fibroscan performed in a one stop 11 clinic. Review patient with results, two to 12 four weeks for with results, and medication 13 ordered according to results, treatment 14 commenced two weeks later, delivery time two 15 weeks. Review patient early in the course of 16 treatment, two to three weeks after starting, to 17 check patient is tolerating treatment, 18 compliance, repeat routine bloods. Further 19 follow-up at the discretion of the treating 20 clinician in partnership with the patient. 21 Review patient 12 weeks after treatment has 22 finished for blood tests to confirm success of 23 treatment." 24 Then in relation to subsequent follow-up 25 post-SVR, he said this:</p>	<p style="text-align: right;">158</p> <p>1 "This depends on the patient's level of 2 disease prior to treatment. If the patient has 3 no or minimal damage to the liver prior to 4 treatment, then the patient is discharged back 5 into the community as no follow-up is required. 6 If the patient has advanced liver disease then 7 they would be followed up appropriately by that 8 service, ie, regular scans for hepatocellular 9 carcinoma and regular monitoring with 10 hepatology. Further later date, blood-borne 11 virus testing is also recommended if a patient 12 continues to engage injecting drug use." 13 That last part is not for present purposes. 14 That was in relation to Wales. Insofar as 15 Northern Ireland is concerned, we have 16 a statement from the Director of Surgery and 17 Specialist Services at Belfast Health and Social 18 Care Trust, Caroline Leonard, and what she has 19 said is this: 20 "The hepatology team in Belfast Trust advise 21 that all new patients with a diagnosis of HCV 22 are offered blood tests [and she's listed the 23 various tests], an ultrasound scan and a 24 fibroscan. Those who have chronic hepatitis C 25 and who are fit for treatment are offered</p>
<p style="text-align: right;">159</p> <p>1 treatment. If treatment is commenced, blood 2 tests are carried out during treatment to ensure 3 liver tests remain satisfactory. At the end of 4 treatment, hepatitis C status is checked with 5 HCV PCR test and again three months after 6 completion of treatment. If the PCR test is 7 negative at end of treatment and three months 8 post-treatment, this indicates successful 9 clearance of the HCV infection. In previous 10 years, it was also the practice of the regional 11 hepatology team at the Royal Victoria Hospital 12 to do a check-up PCR test one year 13 post-treatment. In keeping with practice 14 throughout the UK, this is no longer required." 15 Then in terms of follow-up post-SVR, she 16 says this: 17 "The hepatology team in Belfast Trust advise 18 that patients who are PCR negative after 19 treatment and who have a normal fibroscan are 20 discharged from the hepatology clinic. Those 21 who have an indeterminate fibroscan result will 22 usually have a follow-up fibroscan at least six 23 months after finishing treatment. If the 24 fibroscan is satisfactory, the patients are 25 discharged. Patients who have a fibroscan</p>	<p style="text-align: right;">160</p> <p>1 suggestive of advanced fibrosis or cirrhosis are 2 kept under long-term review at the liver clinic. 3 These patients require an ultrasound and blood 4 test for alpha theta protein every six months to 5 screen for hepatocellular cancer. In addition, 6 such patients have a six-monthly clinic review." 7 Then to complete the geographical picture, 8 in relation to England we have a statement of 9 Claire Forman on behalf of NHS England. Her 10 statement is rather lengthier, so I'm not going 11 to read out all of it. She refers to what would 12 be the ordinary pattern of HCV care and then on 13 the issue of what happens post-SVR, she says 14 this: 15 "It's generally recommended that in the 16 absence of liver cirrhosis, patients with HCV 17 who have cleared the virus with treatment can be 18 discharged from follow-up and no routine 19 surveillance is indicated. Many clinicians 20 perform a single repeat check of HCV RNA status 21 and liver function six to twelve months after 22 treatment to identify the very rare patients who 23 suffer a late relapse, but in the absence of 24 co-morbidities, no follow-up is indicated. For 25 patients with cirrhosis, standard follow-up</p>

<p style="text-align: right;">161</p> <p>1 post-therapy should include a review every six 2 months with an assessment of liver function by 3 blood tests, including a full blood count, liver 4 function tests and usually clotting assessment. 5 A liver cancer screen should be performed with 6 an ultrasound scan and an alpha theta protein 7 assessment." 8 Then there's a reference to differential 9 follow-up depending upon co-morbidities. 10 So the purpose of highlighting those 11 statements, and drawing attention to the fact 12 that they'll be published upon the Inquiry's 13 website is precisely because we have heard 14 people relaying that they have not been 15 receiving follow-up care, and whilst obviously 16 the Inquiry is not in a position to investigate 17 such individual cases, it's hoped that by asking 18 the question of the four nations or parts of the 19 United Kingdom and getting these answers, 20 individuals who feel they have not been 21 receiving the follow-up care that they may be 22 entitled to can use this information to go to 23 their treating clinicians or to their GP and ask 24 to have fibroscans, blood tests and the 25 appropriate referrals.</p>	<p style="text-align: right;">162</p> <p>1 That was the first part of the questions we 2 asked. The second was about psychological 3 counselling and availability or non-availability 4 of psychological counselling. I will start, for 5 reasons that may become apparent, with Wales. 6 Again, the statement of Professor Jones, the 7 Deputy Chief Medical Officer. I should say, 8 these are answers to questions that were asked 9 partly about the availability of psychological 10 services generally, and then specifically about 11 the availability of psychological services for 12 those infected with hepatitis or HIV through 13 infected blood or blood products. 14 The Inquiry in particular drew the attention 15 of those to whom the request was directed to 16 a fund set up in relation to the provision for 17 physical and mental well-being for victims of 18 the Grenfell disaster and asked if there were 19 any similar arrangements to those infected as a 20 result of blood or blood products. This is the 21 position as we understand it to be, or as we are 22 told it is going to be, in Wales. 23 Professor John says this: 24 "Psychological support is provided 25 specifically for beneficiaries of the Welsh</p>
<p style="text-align: right;">163</p> <p>1 Infected Blood Support Scheme through funding 2 provided by the Welsh Government. The Minister 3 announced the provision of this service in 4 March 2019. The Welsh Government, WIBSS and 5 (reading) trust which hosts WIBSS, and 6 stakeholders, work together to produce 7 a blueprint for the psychological services that 8 are required to meet the needs of those infected 9 and/or affected together with their families. 10 A proposal was taken to the WIBSS governance 11 group and approved. The WIBSS psychological 12 support service began seeing beneficiaries and 13 family members in December 2019. The service is 14 continuing to develop its standard operating 15 procedures, referral process, et cetera. All 16 patients who had previously requested such 17 support were contacted and informed about the 18 service. Those beneficiaries or family members 19 deemed to be at high risk were seen as priority 20 by either the consultant psychologist or lead 21 counsellor." 22 Then there's a reference to positive 23 feedback. 24 Then: 25 "This information is provided from the WIBSS</p>	<p style="text-align: right;">164</p> <p>1 website: 2 "A psychology team specifically for the 3 service has been established. From 4 January 2020, individuals registered with WIBSS, 5 their family members and bereaved family 6 members, can access psychological assessment and 7 treatment concerning the emotional difficulties 8 of being given and living with a diagnosis of 9 hepatitis C and/or HIV. The team are aware of 10 the historical context, and have experience of 11 working with the emotional difficulties that 12 have occurred as a result. The hope is that by 13 offering a specialist psychology service there 14 will be some acknowledgment and recognition of 15 the physical and psychological complexity and 16 impact on the quality of life and 17 relationships." 18 So there was a very recently established 19 specialist service for those with whom this 20 Inquiry is concerned, that has just been set up 21 in Wales. 22 Insofar as Northern Ireland is concerned, we 23 again have several statements that will all be 24 published, but the only one I'm going to refer 25 to is again from Caroline Leonard at the Belfast</p>

<p style="text-align: right;">165</p> <p>1 Health and Social Care Trust. She says this: 2 "Prior to January 2019, no dedicated 3 psychology service was available to either the 4 infected or affected patients or relatives 5 associated with the Infected Blood Inquiry. The 6 trust established a working group in 7 September 2018 to consider the implications of 8 Infected Blood Inquiry work as this relates to 9 Northern Ireland. 10 "At an early stage the working group 11 identified a requirement for additional 12 psychological support specifically in respect of 13 the needs of those people in Northern Ireland 14 directly impacted as a consequence of infected 15 blood products. A funding proposal was 16 submitted to the Department of Health and 17 non-recurrent resources were made available for 18 the Belfast Trust to put in place dedicated 19 clinical psychological capacity to meet these 20 needs. A full time band 8A specialist clinical 21 psychologist is currently funded until the end 22 of March 2021. It's anticipated that further 23 recurrent funding to support this service will 24 be considered in due course. The specialist 25 clinical psychologist provides assessment,</p>	<p style="text-align: right;">166</p> <p>1 psychological therapies, liaison and signposting 2 as appropriate for HIV, HBV and HCV infected and 3 affected patients and relatives since 4 January 2019." 5 And she provides a little further 6 information. 7 So again, insofar as Northern Ireland is 8 concerned, it appears that there is some form of 9 specialist service (established a little longer 10 than the Welsh service, but still relatively 11 new) but specialist focused upon those who have 12 been infected and affected through blood or 13 blood products. 14 SIR BRIAN LANGSTAFF: But not specifically 15 mentioning the bereaved? 16 MS RICHARDS: Sir, the statement, I think -- 17 infected or affected patients and relatives are 18 referred to in the witness statement. 19 SIR BRIAN LANGSTAFF: Thank you. 20 MS RICHARDS: So, yes, it does appear to be broader 21 than infected individuals themselves. 22 The position in Scotland is set out in 23 a witness statement from Samantha Baker. It's 24 quite a detailed statement, and so I'm going try 25 and summarise it. I hope I'll do so in a way</p>
<p style="text-align: right;">167</p> <p>1 that doesn't do any injustice to it. 2 So she explains in some detail that those 3 infected and affected by infected blood and 4 blood products can access a range of 5 psychological support and treatment generally as 6 can other individuals within Scotland. So 7 there's the general provision of psychological 8 services as opposed to specialist provision. 9 In response to the question that was asked 10 about whether there was any kind of specialist 11 service or anything equivalent to the steps 12 taken in relation to those affected by the 13 Grenfell Tower fire, the answer was that there's 14 no directly equivalent services in Scotland for 15 people infected or affected in consequence of 16 infected blood or blood products, and she sets 17 out some reasons in that respect which I won't 18 read, but others will be able to read on the 19 website. 20 She does say that as well as the general 21 services that can be accessed through NHS boards 22 in Scotland, there is a haemophilia 23 psychological support service available for 24 patients with bleeding disorders and their 25 family members. It's said that that was</p>	<p style="text-align: right;">168</p> <p>1 initially only available to patients in the 2 Edinburgh Haemophilia Centre but has been 3 available to patients and family members across 4 all of Scotland since 2018. It's staffed by one 5 full-time psychologist and a part-time 6 psychiatrist. They're based in Edinburgh but 7 travel on certain days to other Scottish 8 locations. It's available to all those with 9 bleeding disorders and their families, but she 10 says a significant proportion of those using it 11 are infected or family members of someone 12 infected with hepatitis C and/or HIV but 13 obviously that's a bleeding disorder-specific 14 service that sits within the Haemophilia Centre. 15 Then finally, the position in relation to 16 England is again set out in the witness 17 statement of Claire Foreman on behalf of NHS 18 England. 19 Again, she points to the availability of 20 general psychological services that might be 21 available to all members of the community and 22 not specific to the communities with which we're 23 concerned. She says that: 24 "Many patients requiring specialised 25 services for a disease or condition will have</p>

<p style="text-align: right;">169</p> <p>1 psychological support needs at some point in 2 their care or treatment pathway, and responding 3 to psychological support needs can be an 4 important part of a patient's overall care 5 package. Whilst it's not expected or desirable 6 for each specialised service to have their own 7 dedicated psychological support service it's 8 expected that all services have in place the 9 necessary links and referral pathways." 10 So that's a means of accessing either 11 general psychological services potentially or 12 psychological services that might sit within 13 certain areas of medical practice but not 14 specifically for infected blood or blood product 15 recipients. 16 Then in response to the question about 17 Grenfell Tower service, well, I'll read out the 18 question that was asked and then the answer. 19 The question that was asked was this: 20 "The Inquiry understands that (a) in 21 October 2018 NHS England announced funding of up 22 to £50 million for a new screening service to be 23 put in place to provide long-term support and 24 treatment for people with physical and mental 25 health issues following the Grenfell Tower fire,</p>	<p style="text-align: right;">170</p> <p>1 and (b) a free and confidential NHS service, the 2 Grenfell Health and Wellbeing Service, is 3 available to children and adults affected by the 4 Grenfell Tower fire. Please confirm whether 5 there is any equivalent or similar service in 6 England for people infected or affected in 7 consequence of infected blood or blood 8 products." 9 The short answer to the question is that 10 there isn't any such service in England. 11 There's a longer answer which in fairness to 12 Ms Foreman is a reasoned answer that's set out 13 in the statement. I'm not going to read all 14 of it out. She talks about NHS England's 15 response to Grenfell Tower being part of its 16 emergency preparedness, resilience and response 17 duties under the Civil Contingencies Act and 18 then she says this: 19 "In the case of Grenfell and other incidents 20 that year, local communities witnessed extreme 21 events likely to result in significant mental 22 health issues as well as other health problems. 23 In recognition of this, NHS England issued 24 advice to health services about caring for 25 affected people shortly after the incidents.</p>
<p style="text-align: right;">171</p> <p>1 This advice encouraged greater vigilance in the 2 healthcare professionals who provided a leaflet. 3 Individuals were signposted to use NHS Choices. 4 As the Inquiry has noted, NHS England announced 5 on 9th October 2018 the services it would put in 6 place for the local community affected by the 7 Grenfell Tower fire. These additional 8 arrangements were made as part of NHS England's 9 major incident response in enabling the NHS to 10 return to normal as part of the recovery phase, 11 and in response to prevent future deaths report 12 made by the coroner." 13 She refers to a coroner's report in relation 14 to the Grenfell fire which noted that many of 15 those affected by the incident suffered 16 emotional trauma and harm and were therefore 17 likely to need appropriate mental health 18 support, and then says this: 19 "Whilst services for mental health, 20 including post-traumatic stress disorder and 21 respiratory conditions, are generally available 22 via the NHS for all patients, the services put 23 in place for Grenfell were therefore in response 24 to the specific and additional needs of the 25 Grenfell community. This was consistent with</p>	<p style="text-align: right;">172</p> <p>1 the principle that NHS patients with equal need 2 should have equal ability to access services 3 regardless of how those needs arose. In the 4 same way, ill patients with hepatitis C have 5 been able to access NHS services and treatments 6 on the basis of need rather than differentially 7 based on how those needs arose." 8 Then she refers to both general and more 9 tailored psychological services being in place 10 for individuals affected by diseases generally 11 through existing networks. 12 So that's the response in relation to 13 England and, as I say, those materials will be 14 published on the Inquiry website if not today, 15 then early next week. 16 SIR BRIAN LANGSTAFF: Thank you, Ms Richards. 17 This is the time when I have previously and 18 I will again reflect on the session of evidence 19 that has just finished and look forward to what 20 comes next. So first, reflection. 21 You may think it follows on, perhaps, 22 a little from what's just been said. Last 23 November, at the close of the first set of 24 hearings during which individuals who have been 25 infected and affected told their stories, I drew</p>

<p style="text-align: right;">173</p> <p>1 together some of the themes that have been 2 explored and, in particular, I said this and 3 I make no apology for repeating it now: 4 "A repeated theme has been the often and 5 unanswered call for help and psychological 6 support for those suddenly facing what has 7 seemed an unfair death sentence with all its 8 side effects on partners, friends and family, or 9 the gruelling courses of treatment they have 10 undergone with their own side effects. It is 11 appropriate, therefore, that when we begin our 12 next set of hearings" -- remember, I was talking 13 then last November, so that's these hearings 14 we've now just finished -- "we shall hear in 15 particular from experts on psychosocial and 16 psychological impact as well as from experts on 17 hepatitis, HIV, blood and bleeding disorders. 18 This evidence will help place what we have 19 already heard in a wider context, and prepare 20 for the hearings with decision-makers which will 21 follow." 22 There can be no doubt, let me repeat that, 23 no doubt, that what we have heard this week has 24 underlined that message, written it in bold, set 25 it out again in starkest clarity. It's done</p>	<p style="text-align: right;">174</p> <p>1 more than that. It's added the voices of those 2 who spoke via the intermediaries we heard on 3 Monday and putting those voices together with 4 the near 200 or who spoke last year directly to 5 those who are here, or watching online, more 6 than 250 testimonies have emphasised the need 7 for the message about psychological support to 8 be heard. 9 I can tell you that I have now read over 10 four times that number of written statements, 11 which have in their own individual ways, added 12 to the force of what has been said orally. But 13 what makes me raise this again in such strong 14 terms as I do now is that we have now heard that 15 scientific expertise of the highest standing 16 fully supports that view. 17 We shall all take our own messages from this 18 week of evidence, but what I personally would 19 like to highlight is this: it must be the case 20 that anyone who has given a life threatening 21 diagnosis may need support and should be offered 22 it, and so too their families may need support. 23 Yet the very fact that number of people with 24 chronic hepatitis B or chronic hepatitis C or 25 HIV infection chose to describe their resulting</p>
<p style="text-align: right;">175</p> <p>1 life-threatening illness and need for treatment 2 to those around them as being "cancer" rather 3 than hepatitis or HIV, shows that the isolation 4 in which they had to bear their illness added 5 a dimension beyond even cancer. Add to that the 6 fact that so many clinicians advised them to 7 tell no one. In effect, medical advice to live 8 a lie, or if that's too strong, at least to 9 limit the social network that might otherwise be 10 there to support those who are suffering. 11 This shows that the stigma of having one or 12 more of these blood-borne infections was not 13 just something the sufferers alone recognised, 14 their doctors did too. 15 Add the sad fact that the evidence suggests 16 that there still remain pockets of ignorance and 17 prejudice amongst, of all people, NHS staff. 18 Add to that the worry. "Can I pass it on? Am 19 I infecting those dear to me? Have I already 20 done so? Dare I risk becoming a patient?" Then 21 add the effects, the direct effects of the 22 viruses on mind personality, and the effects of 23 treatment, and if on personality, on 24 relationships. All these factors make it clear 25 that there was a need for there to have been</p>	<p style="text-align: right;">176</p> <p>1 effective, knowledgeable, expert psychological 2 support services on offer. 3 The evidence thus far has underlined that 4 those who received infected blood and their 5 families have suffered in all the ways I've 6 highlighted and many, probably most, have 7 suffered all the more because they had no such 8 support. 9 Now, I'm delighted to acknowledge the very 10 significant advances that there have been in the 11 treatments for hepatitis, particularly 12 hepatitis C, and HIV infection, and we heard 13 today in thalassaemia and sickle cell and it's 14 anticipated that genetic advances may help 15 further. But what we have also heard this week, 16 however, has told us that though hepatitis C 17 itself can be cured, chronic hepatitis B cannot 18 yet be, nor can HIV. 19 Anyone with either of those conditions must 20 go on taking tablets for the rest of their 21 lives. They may fear what the future brings. 22 Their trust in doctors may be shaky because of 23 the source of their infections. 24 We have heard that the effects of past 25 infection and past treatment don't simply</p>

<p style="text-align: right;">177</p> <p>1 disappear. A damaged liver does not cease being 2 damaged overnight because the virus that caused 3 it has cleared. Personality and mental function 4 may be permanently affected and we have heard 5 that people are still scared of the way others 6 will react to knowing that they have the 7 disease. Hence the large take-up of the 8 services of the intermediaries from whom we 9 heard, and some find it difficult to access the 10 medical services they need for other conditions 11 because they have experienced stigma amongst NHS 12 staff in the past.</p> <p>13 Now, every day this week, as I've heard it, 14 we have heard the same message: that support is 15 needed, not just from those to whom the 16 intermediaries gave voice, not -- we haven't 17 heard it just from the psychosocial experts but 18 we've heard it also from leading experts in 19 hepatitis and leading experts in HIV, and today 20 we've heard that psychological support remains 21 at best patchy in some parts of the country.</p> <p>22 So it's for those reasons that I would like 23 to draw the attention publicly now of NHS 24 England and hospital trusts and boards 25 throughout the country to the fact that the need</p>	<p style="text-align: right;">178</p> <p>1 for specialist treatment by professionals who 2 have a special understanding of infected blood 3 and blood products has not gone away, now that 4 there is greater success in treatment of the 5 underlying conditions, that there is a need to 6 ensure that the standards of follow-up of those 7 who have cleared hepatitis C but have been left 8 with a compromised liver are maintained in 9 accordance with what the experts have set out 10 this week, that the support of not only those 11 infected, but their families, need special 12 attention, and that those who have lost 13 a partner, son, daughter, brother, sister, 14 mother, father, grandparent or close friend must 15 not be ignored.</p> <p>16 I should add that I mentioned NHS England 17 not because I'm being parochial but because, as 18 you've just heard, both Northern Ireland and 19 Wales have told us that they have started to 20 answer this call by providing services bespoke 21 to those who have been infected by blood and 22 blood products. If they have opened the door to 23 treatment and support, I would hope -- indeed 24 expect -- to see England and Scotland fully 25 follow suit.</p>
<p style="text-align: right;">179</p> <p>1 Though I have had no detailed dissection of 2 any figures as yet, the evidence thus far 3 suggests that the outlay of public funds would 4 not be great, but also that expenditure on 5 support and screening will save money in the 6 long run because it will help improve and 7 maintain health.</p> <p>8 The evidence this week from undoubted 9 experts of the highest calibre has demonstrated 10 that the health of the mind affects the health 11 of the body and the health of the body affects 12 the health of the mind.</p> <p>13 I hope to be able to acknowledge in the 14 final report that proper support and follow-up 15 will by then be in place across the UK. So much 16 for reflection.</p> <p>17 Looking forward. What comes next? In June 18 and July this year we shall start hearing about 19 the knowledge of risk, with particular reference 20 to the Haemophilia Centres and the clinicians 21 who practised in those centres.</p> <p>22 Precise details will follow in due course. 23 This is exactly as I'd anticipated at the 24 start -- or the end, I should say -- of our 25 hearings last October as I've just read out to</p>	<p style="text-align: right;">180</p> <p>1 you at the start of my reflection. We are on 2 course as we had planned to be, and I hope 3 you've seen from this week that it fits together 4 to give us a proper basis for approaching what 5 we need to do in June and July starting then.</p> <p>6 For those of you who wish to come back and 7 hear that, I look forward to seeing you again. 8 Otherwise, can I just say that I wish you a very 9 safe journey home. Thank you.</p> <p>10 [Applause]</p> <p>11 (4.05 pm) 12 (Adjourned until a date to be confirmed in June) 13 14 15 16 17 18 19 20 21 22 23 24 25</p>

<p>DR GOODING: [56] 6/12 26/3 27/10 27/17 27/24 31/16 32/18 34/25 36/18 39/4 42/4 42/20 44/6 45/22 50/20 59/12 60/6 60/9 60/12 60/16 63/1 67/24 68/6 68/8 69/7 70/1 70/5 70/9 71/7 73/17 74/18 74/23 74/25 75/4 75/24 76/4 78/10 78/23 79/4 79/7 79/17 82/22 83/17 84/6 84/19 86/10 86/16 89/8 90/21 93/13 93/22 93/24 146/23 147/7 149/1 151/13</p> <p>DR MARSHALL: [32] 6/4 126/6 127/9 128/1 128/10 130/3 130/8 131/1 131/6 131/9 131/13 131/16 131/20 131/25 132/7 132/9 132/14 134/6 134/22 135/18 136/4 137/24 138/4 138/7 139/5 139/7 139/9 139/14 139/16 140/20 142/2 152/11</p> <p>DR RYAN: [26] 6/23 35/18 94/19 99/9 99/23 100/12 101/12 101/24 102/2 102/7 102/23 103/8 104/9 104/16 105/3 105/15 105/17 109/12 109/19 109/21 111/22 112/25 113/17 114/12 122/3 145/16</p> <p>DR SEKHAR: [12] 5/4 24/6 24/8 25/2 41/8 85/13 85/15 103/21 105/1 114/24 142/21 152/17</p> <p>DR TUNSTALL: [99] 7/8 27/16 28/17 29/2 29/10 30/13 32/19 33/17 33/23 34/9 36/11 37/8 40/6 40/23 41/7 41/22 42/10 42/19 44/7 45/15 46/16 48/3 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'90s [1] 125/18 '94 [1] 114/14 '95 [1] 5/10 '96 [1] 7/11</p> <hr/> <p>1 1 per cent [2] 31/19 33/14 1,000 [2] 33/19 99/22 1,921 [1] 99/13 1.04 [1] 94/10 1.3 [1] 75/20 10 [6] 9/10 74/1 108/3 111/1 116/6 151/7 10 years [3] 10/6 24/18 119/12 10-minute [1] 143/16</p>	<p>10.30 [1] 1/2 100 [5] 33/18 33/19 33/21 34/23 78/6 100 per cent [5] 33/13 33/15 34/6 35/6 35/7 100th [1] 33/14 11 [1] 116/6 11.33 [1] 47/20 12 [5] 79/24 87/7 88/9 156/2 157/21 12 hours [1] 60/19 12.04 [1] 47/22 13 million [1] 66/22 13,675 [1] 99/15 13.4 million [1] 66/14 150 [2] 34/2 34/6 16 [1] 91/6 19 [1] 75/19 1950s [3] 123/11 125/9 128/3 1952 [1] 127/9 1956 [1] 127/9 1957 [1] 127/18 1970 [2] 3/20 3/21 1970s [5] 4/2 4/15 41/10 63/19 125/13 1980s [5] 4/2 4/16 125/18 128/13 134/25 1981 [1] 7/1 1982 [1] 5/8 1983 [1] 131/1 1985 [1] 5/21 1989 [1] 7/19 1990s [3] 101/15 113/8 137/16 1993/4 [1] 133/14 1994 [8] 7/3 128/18 129/25 137/24 137/25 138/2 139/2 141/13 1994/5 [1] 137/25 1995 [1] 5/20 1996 [1] 5/22 1998 [1] 7/23 1999 [1] 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