IN THE COMPETITION APPEAL TRIBUNAL

Case No: 1524-1525/1/12/22

Salisbury Square House
8 Salisbury Square
London EC4Y 8AP

Monday 6th November – Friday 1st December 2023

Before:

The Honourable Mr Justice Marcus Smith
Eamonn Doran
Professor Michael Waterson

(Sitting as a Tribunal in England and Wales)

BETWEEN:

Appellants

Pfizer Inc. and Pfizer Limited & Flynn Pharma Limited and Flynn Pharma (Holdings) Limited

V

Respondent

Competition & Markets Authority

A P P E A R AN C E S

Mark Brealey KC, Robert O'Donoghue KC & Tim Johnston (Instructed by Clifford Chance LLP) on behalf of Pfizer

Jemima Stratford KC, Tom Pascoe & Alastair Richardson (Instructed by Macfarlanes LLP) on behalf of Flynn

Josh Holmes KC, David Bailey, Jennifer MacLeod, Julianne Kerr Morrison & Conor McCarthy
On Behalf of the Competition & Markets Authority

Tuesday, 14 November 2023

(10.00 am)

(Proceedings delayed)

(10.13 am)

THE PRESIDENT: Good morning.

MS MORRISON: Good morning, sir, I will be leading Professor Sander's evidence this morning and then cross-examining Professor Walker. I think what we have agreed now is we will go straight into Professor Sander's teach-in, unless the Tribunal has any questions or housekeeping this morning?

THE PRESIDENT: No, not for us. We can go straight into the evidence in that case, thank you very much.

PROFESSOR LEY SANDER (affirmed)

THE PRESIDENT: Professor, good morning. Do hand the card back, make yourself comfortable, have a seat. You should have some water there, and I hope that someone has placed the materials that you need before you, but I am sure counsel will introduce those to you.

Teach-in by PROFESSOR SANDER

MS MORRISON: I think you should have in front of you a bundle of expert reports, and if you could find tab 6 in that bundle?

A. Yes.

Q. You should find there, one hopes, your expert report.

A. I'm afraid I have not changed name. It is Susan Smith here.

Q. I think you have the wrong set of expert reports. It should be behind you there, I'm sorry. It should be XE/4 behind you on the shelf. Let us see, second time lucky, tab 6 that bundle hopefully will have your expert report. {XE4/6}

A. Yes.

Q. Could you go to the last page, page 17 of that report. {EX4/6/17}

A. Yes.

Q. Can you confirm that that is your signature at the end of the page?

A. Yes.

Q. First I am going to ask you a few questions about your report.

Could you confirm that you have made clear which facts and matters referred to in your report are within your own knowledge and those which are not?

A. Thank you. I am a professor of neurology, clinical epilepsy, I am the holder of the only chair in epilepsy in the country and the first in Europe, I have been in this post since 1999.

I have quite a large track record in terms of treating people with epilepsy, my only clinical

expertise is epilepsy, I do not do other work. I am the head of the Department of Clinical & Experimental Epilepsy at UCL, I am a fellow of the Academy of Medical Science, and of the European Academy.

I see an average -- I found out recently that I have 1,700 active patients, and I see, in a week, about 40 people with epilepsy in my clinics.

Q. I am just asking about your report, Professor Sander, before we move on. Can you just confirm that the opinions expressed in your report represent your true and complete professional opinions on the matters to which they relate?

A. Yes.

Q. First, Professor Sander, just going back to the basics, can you outline for the Tribunal the goals you are seeking to achieve in treating patients with epilepsy?

A. Thank you. The objective of treating someone with epilepsy is to give the person the quality of life, as soon as possible. Of course, this means different things for different people, but a part of what I would think is very important is to make this person seizure-free without causing them any side effects or problems, without being an obstruction in their life, and try to reduce the morbidity and mortality, premature mortality that is associated with epilepsy, particularly

chronic epilepsy, so that is a very important thing that we need to have a holistic approach to the person we are looking after.

Q. Can you provide the Tribunal with an indication of how many patients were taking phenytoin in the 2012 to 2016 period and then now?

A. I would not be able to tell you numbers because I do not think that anyone will have that exact data, but probably somewhere around 10% to 12%, and this number has dramatically gone down to the point that in 2022, prescriptions for phenytoin amongst anti-epileptic drug has been less than 3%, so we have seen this dramatic fall.

This is also very evident in my department where we have seen the numbers going down to a point that in the last year, only 11 people were started -- on a population of 9,000, 11 people were started on phenytoin.

Most of these prescriptions were by three consultants and the consulting body, depending on how you count, is 18 or 19, but only three of the consultants actually prescribed, and one of them prescribed more than half of what was prescribed within the department.

So I think that the numbers, everyone has seen this

quite dramatic drop in the number of people that have been on phenytoin. Most people taking phenytoin are what are called legacy patients. These are patients that have been started in the past when phenytoin was one of the options available and have stayed on this medication over time.

THE PRESIDENT: Regarding these legacy patients, presumably you could shift them to another form of treatment?

A. That is correct, and I think that the policy would be my view is that if there is any indication that they are having problems and you can try to measure this, draw blood tests or a bone density check, if there is no reason, then, you know, you probably would keep them on stable, because there is always the risk if someone is seizure-free on a particular medication that seizures could come back, so I think that that is the -- however, I have a very low threshold in terms of people having problems, having side effects, and it is very common with this drug, the drug we are talking here, so I have done a lot of changes over time, most of them have not been a problem, but sometimes things have gone wrong, so -- in terms of seizure freedom, and the person then opts to go back to this drug.

THE PRESIDENT: To what extent will your predisposition, the very low threshold you have referred to, be overridden

or governed by patient choice?

A. Patient choice is the most important thing. People are allowed to make wrong decisions and I think we need to respect them, and if people have capacity, then if their decision is that they would like to stay with this drug, we need to respect that, and that is the case.

Sometimes if I were in the shoes of this person I would not take that decision, but I respect their decision, and that would be my approach.

THE PRESIDENT: In practice, you will only see, given your significant expertise, you will only see legacy patients on phenytoin when they have problems.

A. That is correct. Most legacy patients, they will not be seen at tertiary care, they might be at secondary care, or they might be, which is even more common than we would like, they are just seen at primary care, that is by GPs. When there are problems, or, for instance, when there is a consideration to come off medication, or there is a recurrence of seizures, then they might be referred back.

One common thing that people are referred back is when they have breakthrough seizures, that is the time that you see people being referred back, and as Professor Walker said yesterday, a major issue we have in epilepsy is non-compliance or non-adherence to

treatment. This is a very common, more common than we think, and doctors not always are aware of that, because patients will not actually inform.

So they might have forgotten, they may have a break of routine. When the only reminder of someone's problem is the fact they are taking tablets, if there is a break of routine, then people may forgot to take the medications they should be taking, and there might be breakthrough seizures.

In my experience, this is probably the most common reason why people have breakthrough seizures: when they do not take the medication.

THE PRESIDENT: Thank you.

I do apologise, Ms Morrison.

MS MORRISON: No, please, any questions from the Tribunal are very welcome. Do you prescribe phenytoin, Professor Sander?

A. I do not prescribe phenytoin unless it is needed, there is nothing else available, and I must say I have not prescribed phenytoin for a long time.

I probably have not started a de novo patient phenytoin well over ten years, probably more, and in the last year I have prescribed it to one patient, and I know that as a fact.

So I tend to avoid this drug. We heard a lot about

this drug being a third option, third-line drug, but as there is no fourth-line, in my books third-line is last option, so it is a last resort drug. There are not that many drugs and guidelines as a fourth or third option, phenytoin being one of them, but I would use something else if I have to get there. However, I think it is very important that we understand what is happening in epilepsy. Professor Walker mentioned yesterday the demographic changes we have seen, and these are very clear.

We first described this or brought this up in 1994, 1995, and this is very evident, that we have seen a major change in the demographics, and I would be -- I am quite clear that the number of people that nowadays have chronic epilepsy has dramatically fallen because the natural history of a number of epileptic syndromes have changed.

If you go to any tertiary centre in the western world and you ask if they have seen something that we call hippocampus scleroris, this is a specific epileptic syndrome and it is epilepsy of the mesial temporal lobe, associated with what is called scleroris of the mesial temporal lobe. This condition has fallen dramatically and we have no clue why this happened. There are some educated speculations why it has happened. So that

condition has gone.

Another condition that seemed to have gone is what is called double cortex syndrome. Hardly see them these days. Of course, they might be still seen in other places, in other situations. Like Professor Walker mentioned yesterday, we may have different demographics for epilepsy in resource pool settings.

But in the western world -- and the reason we know about the fact that the natural history of hippocampus scleroris has changed, it is because that is one of the conditions in epilepsy that are amenable to surgical treatment.

So twenty years ago, the majority of people we would be operating to cure their epilepsy had this condition. Nowadays, it is extremely rare that we see anyone, and when they come, often they come referred or there are specific reasons, but it is not something we see anymore, and this is the consistent pattern in Australia, in Germany, in the US and Canada. So we have this change.

The other thing which is important is that we had a drop in epilepsy in childhood. There was an increase in the first year of life, and the reason that this is likely to be the fact that people that had a major insult to their brain whilst they were developing, or at

the time of birth, they are surviving now, and if you have any insult to the developing brain, epilepsy is a -- tends to be a problem.

So the first year of life, there was an increase in epilepsy, in the first year of life the incidence of epilepsy is around 100 per 100,000. In the general population it is 50 per 100,000 as we heard yesterday, and this has not changed, but what has changed is the proportion.

So nowadays the group and the population with the highest incident is the elderly, and the elderly, if the older someone, more senior, the higher the risk, to the point that if you are the age of 80, the incident is around 330 per 100,000.

One thing that is good about -- well, that is not the right way to put it, but epilepsy in the senior citizen is very easy to treat. People tend to respond to a sniff of any drug, and the concern is actually tolerability, it is patients being able to take that without problem, side effects, and in this population, it is very important to remember that multi-morbidity is a problem, and polypharmacy, people taking many drugs and this raises the question of interactions, but this is why I think that a number of people that are coming with so-called bad, intractable epilepsy has gone down,

and this is something we need to keep in mind.

THE PRESIDENT: Thank you. Just to pick up on a minor point -- that was a very interesting answer, but a minor point: I do not think there is a difference between yourself and Professor Walker that phenytoin is a third-line drug. Where I think there may be a difference is that Professor Walker puts phenytoin higher up the third-line running order than you do.

The sense I am getting is phenytoin is pretty much at the end of the running order for third-tier treatment, whereas Professor Walker -- and I am sure he will be asked about this in cross-examination -- but Professor Walker accepting that it is to be used later down the line than first-line, second-line drugs, puts it rather higher than you do.

Now, that sort of disagreement is something which, frankly, we would expect with experts because these are difficult questions of treatment of a very serious condition.

I wonder, though, if you could articulate for our benefit the nature of your disagreement with Professor Walker in the sense that obviously you disagree, but do you regard it as a difference between expert professionals where you just have a different view to him, he has a different view to you, or do you

go further than that and say he is wrong?

A. Well, who am I to say someone is wrong, that is the first thing, I think it is important. What I do is I have my practice, it is very much preventative, it is looking for the person, preventing rather than managing problems.

Also, one of my major research interests is the premature mortality of epilepsy, and that is a big problem, the biggest load of epilepsy is premature mortality, and this is something that we should do something about, and we know that the major drivers for this premature mortality is co-morbidities, and many of these co-morbidities could be prevented, for instance, cerebrovascular disease, we have for instance respiratory issues and other things, and my educated guess, although I accept that we do not have a smoking gun yet, but every single evidence, circumstantial evidence, point to the fact that enzyme inducers, strong enzyme inducers are not good for your health. They make the liver work overtime and as a result of that, they will increase the risk of co-morbidities.

I must say here for the record, my problem with enzyme inducers is not only with phenytoin, but I do not like other strong enzyme inducers, for instance, carbamazepine I hardly use and phenobarbital which is

another drug that is a strong enzyme inducer.

I think it is fair to say that phenytoin has some other problems, for instance, the non-linear kinetic, that can be a problem, and it can be quite tricky in terms of sort of getting the proper management in a situation where you sometimes do not know someone is taking the drugs, a number of things.

So I would think that my view is not limited to phenytoin in terms of -- I think that enzyme inducers are my big problem, and if we were to avoid -- and I am very much in risk avoidance, and if we are to avoid risk and we have so many circumstantial evidence pointing out that there is a problem when people take enzyme inducers because their liver is working over time, then I would try and avoid that.

So I do not prescribe carbamazepine unless I need to. I tend to avoid phenobarbital, but I need to say that I would use phenobarbital ahead of phenytoin and the main reason for this is it has to a linear kinetic.

THE PRESIDENT: But I think -- do correct me if I have this wrong -- I think you are saying that the sensitivity of other physicians in your field to enzyme inducers might be different. You are perhaps on the very sensitive side of the scale and others would be less sensitive and more sensible of the advantages of, let us say,

phenytoin?

A. Yes.

THE PRESIDENT: You would disagree obviously, but you would not say that was outside the realms of reasonable disagreement in terms of how to manage a patient?

A. I think that there is a strong body of consultants, expert, that would avoid enzyme inducers. The majority, and I think worldwide, enzyme inducers, because they are cheap, they are still sometimes the only non-nihilistic approach to treat epilepsy, but this is not the case here.

So last -- two years ago there was a debate in neurology congress where I was presenting the case to avoid enzyme inducers, and there was a vote before, and it was a third saying, you know, let us avoid, we should avoid enzyme inducers, and the other two-thirds said, no, we should not, but at the end of the debate things -- there was another vote, and it more or less balanced out.

So I think that people, once they hear the problems, they are more likely. We do not discuss on a day-to-day basis the problems that result from enzyme inducers, but if we want to avoid risk, and I think that risk is an issue, if we can prevent a problem, we should do that, and that is why I am very happy to say I am strongly

against enzyme inducers. That does not mean to say I will not use them, but I try every time something that does not have that problem.

There are enzyme inducers that are stronger than others, so this is sometimes we might even consider using one that does not have the same strong, and we heard yesterday that carbamazepine is probably the stronger, and I accept that, enzyme inducers in my books, they are a problem, and I would like to see a world without enzyme inducers.

They are not a problem if they are used in the short term, but if they are used in the long term, there is plenty of evidence that within months, people's cholesterol goes up, anti-inflammatory markers go up, and they normalise once people come off an enzyme inducer, the evidence is quite clear, and this should be really a red flag for us, and this is why I have my views on this.

THE PRESIDENT: Thank you.

MS MORRISON: Professor, just picking up on one of the points I think that the President was putting to you and you were responding to, I know in fact Professor Sander was in court all day yesterday, because I was a bit too gung-ho in making sure he was here on time for teach-ins and things, so you heard most of Professor Walker's

teach-in, and he referred to a straw poll of colleagues that he had asked about using phenytoin, and I think the implication really was that you were an outlier in your views on phenytoin.

Are you an outlier? What is your experience?

A. I have not done a straw poll, but I feel that I am not so much of an outlier. For instance, in my own department, hardly anyone uses phenytoin. You know, that on itself is a party political statement because, you know, this is the biggest epilepsy service in Europe by a long way in terms of the number of people, and we do not -- we are supposed to have the most severe patients with epilepsy, and we have prescribed this to such a small number that, you know, I do not think that I am an outlier.

This morning, I came across a senior colleague, and I asked him this question, I did a straw poll, and he looked at me amazed and he said: oh, you must be having -- you know, you should not be using phenytoin, so, you know, I was really relieved that this was what my colleague said.

THE PRESIDENT: Sorry, Professor, I interrupted you, do finish your answer.

A. Yes.

THE PRESIDENT: I just had a question about what you meant

when you said "biggest epilepsy service in Europe". Is that the NHS treats more epileptics than anyone else in Europe, or more with phenytoin? I just want to understand what you meant when you said --

A. Phenytoin is not in the formulary in many countries. It is actually -- in Scandinavian countries it is not part of the formulary. There is a process you can prescribe it and it is rarely prescribed. The same in the Netherlands, countries that I know. But going back to the service, what happens within the NHS is the biggest concentration of service. So you could argue that the National Hospital for Neurology is more than a tertiary centre. So it is the last port of call to people with chronic epilepsy around -- coming, and we get referrals from all over the country, and the numbers, they are quite high, and that is what -- the throughput of patients is the highest, and, you know, this has been the case for well over twenty years now.

THE PRESIDENT: I see, so what you are really referring to is a concentration of expertise because you are funneling patients to a particular tertiary provider such that they are treating so many patients that one gets -- I mean, one should not use the phrase "economies of scale", but one is getting economies of knowledge, if you like. You are building your knowledge because you

are doing more of this very important treatment.

A. Our service also has the only assessment unit attached to the unit which is the Chalford Centre where I am the medical director, and that is really the end of the journey, it is a last port of call to someone that has chronic epilepsy in this country, and what we do there is diagnose, change drugs, consider the next steps for a person. So that is why we also get referrals.

THE PRESIDENT: I understand, thank you.

MS MORRISON: Professor Sander, you have already referred to the fact that phenytoin is an enzyme inducing drug, but I just wonder if you could give for the Tribunal your overview of the clinical package offered by phenytoin, the side effects, etc.

A. Well, the package is a drug that there is no -- I do not think that I have a problem that it does work for some people, but its toll on people is in terms of the enzyme inducer, the propensity for drug interactions, chronic side effects coming out of the enzyme-inducing properties of the drug, and making it sometimes difficult to use. I feel that in that package, it is not a package I would like to have myself exposed, and I think that is a very important test a doctor should always make: would I want to use this? I am very clear that I would only use it if there is no other option,

and that is what I should do for the people I see.

So the package is -- the package I would like to have is the one that will give me the best chance of achieving the outcome, which is no seizures, but at no cost of side effects, and I think it is a really -- I see patients that come with letters from -- saying this person is well controlled, no problems, but then when you talk to them, they are putting up every morning with about half an hour of double vision or blurred vision. Is this something that you would put up, and I do not think that I would put up with that. So I think that that is time, even if this person is seizure-free. Of course at the end of the day they may choose to stay on that and to pay, as someone told me, I am paying the price of being seizure-free, I tried several drugs, and nothing worked, but this one I am okay, and I respect that, but I would not want to have double vision for half an hour every day after I take my drugs.

THE PRESIDENT: Just as a matter of fact understanding the weight of this, how in general terms amenable to experimentation is your epileptic? Let us suppose you have someone, just as you have described it, who is on phenytoin, has been stable for many years in the sense that there is no seizures, but they have double vision

for half an hour or so in the morning and they do not like it. Would you say that generally speaking epileptics are risk-averse, they prefer to hang on to the stability of no seizures, or when they have got someone who obviously knows what they are doing saying: look, I think we can get you the stability without the side effects, but there is a risk. How open to that risk are they?

A. I think there is a whole range of people with different approaches to this. Some people are extremely sensitive and they will have issues with most drugs, whilst there are some people that are very resilient, and I always admire the resilience of some people with the problems they have arising from their epilepsy and problems that are heterogenic, which is problems that we impose the patient with our treatment, but it is always a question that we need to identify with the patient, you know, is this something, and I would probably say that it is half and half in terms of people not wanting to have problems whilst other people are more resilient to the problem and do not want anything that would, let us put it that way, risk a recurrence of their seizures, if that makes sense.

THE PRESIDENT: No, that does, thank you.

Ms Morrison, I have no desire to tread on your toes,

so if you are coming to it --

MS MORRISON: No, go ahead, sir.

THE PRESIDENT: I am not going to ask the question because I will wait, because you will put it better than I am, but are you going to be taking the Professor, as part of his teach-in, to the MHRA guidance on anti-epileptic products and change?

MS MORRISON: I was going to ask him about continuity of supply, sir.

THE PRESIDENT: Then I will bide my time.

MS MORRISON: There are only two questions before that, sir, so we are almost there.

The first question I wanted to also cover is we have talked a lot about phenytoin, Professor Sander. Can you give the Tribunal an overview of a couple of the drugs that you see as being higher up the chain? What is the package that they offer in terms of side effects, interactions and so forth?

A. Is this drugs in the armamentarium, the 20 or drugs we have?

Q. Yes, just a couple of the other examples, perhaps first-line or second-line, just to give the Tribunal a sense of the comparison.

A. Yes. The drugs that we use I would use as first line, we have heard about them, referred to them several

times. One is a drug called lamotrigine, the other is a drug called levetiracetam. They do have side effects, they do have problems, but they are overall a much lower risk of problems. For instance, lamotrigine has a risk of an allergic reaction that affects about 3% of Caucasians and some ethnic groups it is a little bit more or less, and this is something that we would be flagging up to people, and I always give patients a choice of this through drugs, we go through the pros and cons and then we take a joint decision, but at the end of the day the person has to choose. Some people do not have a problem risking a skin rash, they know that if that happens we need to stop it.

There is also the issue that a lot of my colleagues tend to, let us put it that way, scare patients about a skin rash. Skin rashes happen all the time, and there is good evidence that most drugs, people come off drugs due to skin rash, due to rashes that has nothing to do with the drugs, it is just because we have rashes all the time.

So that is one option. The other option that I -- and I would take both drugs to a desert island if I had to, the other one is levetiracetam. It does not have an allergic side effect, it is an interesting drug in the sense that it is absorbed and almost entirely it is

greeted unmetabolised, so it does not have any scope for interactions because it is greeted unmetabolised.

However, up to one in ten people will develop side effects that are either feeling very lethargic or they could have some behavioural problems, getting irritable, flying off the handle very easily, and so you put the options for the person in front of you, which one would you like, and some people are not afraid of the skin rash, but some people are not afraid of behavioural problems, but we already have a plan, and we know that in population terms, 50% of the time that you give a drug to a person with epilepsy, regardless of the drug, you get a good outcome because we are treating the natural history. You know, for a number of people, epilepsy is a self-limited condition, so I am not saying here we should not treat because epilepsy might be self-limited or benign, however, the seizures are not.

So a person may grow out of their seizures, as sometimes we hear from old ladies, but they might have seizures before that goes away, and as a result of that, they might come to harm because when they have a seizure at the wrong place at the wrong time. So I think that I am not saying we should not treat, but in population terms makes no difference which drug we try first time.

So all drugs seem to have the same outcome. Of

course, what we do not have is how many people would go into remission if we do not use a drug, and it would be unethical to do this trial. However, evidence that we have gathered from developing countries and from certain situations where people choose not to be treated the number of people that will go into spontaneous remission is somewhere between 30 and 50%. The problem is therefore we know that some people will have a good outcome, however, they might come to harm as a result of a seizure. So I would definitely consider treatment, and in this sort of population it would be definitely I would use levetiracetam and lamotrigine, and then we would be moving on. I think it is fair to say that in terms of cognition, these have the drugs that have the best results. I think that a lot of drugs, they start to having problems that will somehow affect the person's ability to conduct their life, so I think that it is important that we consider cognition for the person, and this is why I would use these drugs as first-line, and then we have, depending on which country you are or which jurisdiction, we have now 29, 30 drugs, so it is a little bit sometimes of a maze to go around all these drugs, although it is fair to say that some of them have orphan drug indications, so they are specific for some areas.

We know that some drugs for some seizure types we should avoid, but, you know, this brings us back to the fact that most people, most people, they respond to the first drug and the second. They do not respond to the first drug, you try the one that was the other one, and if that does not work, we can then move on from there.

MS MORRISON: Professor Sander, when might you use phenytoin tablets as compared to capsules?

A. In my view it is very similar to Professor Walker on this. The important thing is that once someone is started, ideally they should start -- they should carry on with the same tablet or capsule. Ideally for phenytoin that does not apply to others, with the same brand or generic or same formulation. I think that I heard a lot about continuity of care here yesterday. I think what we are talking about is consistency rather than continuity.

Professor Walker mentioned that he gets phone calls from people that have run out of a tablet because it is not available. That is continuity of supply. This is when you do not actually get a drug because it is not available.

Now, when you stick to the same drug every time, the same -- exactly the same, that is consistency. People with epilepsy, they do not like, you know, getting

different colours, different shapes of tablets, different boxes, and when some of the lamotrigine for instance and levetiracetam went generic they got different names, we also around that time, we had an epidemic of parallel imports, so people were getting different drugs, sometimes exactly the same drug, just in a different package, in a different language on the box, and that would actually create quite a lot of, let us put it that way, concern to people, and this is around the time that we had the guidelines about sticking, the group 1, that we should stick always to the same formulation.

How is this actually implemented out there, I do not really know, I am not a GP, I am not a pharmacist. Some patients, sometimes just like Professor Walker said yesterday, they come and they show you capsules and tablets, and 25mg capsule, 100mg tablet, and it does not seem to make that much difference, but the risk is there. So we need to -- because the way that generics are done, they do not have to be exactly the same bioavailability. There is this rule of 80, 125, so when you have an originator drug, when someone brings out a generic, they have to show that the area under the curve and the max concentration needs to be within the confidence interval of 95, 80 to 125.

In the case of some drugs it might mean a 36% difference, if someone -- and this is why it is very important, this consistency in phenytoin. The risk is there that if someone is very near saturation point, if they change from a brand or a generic or vice versa, they might actually have problems, and this is the concern.

I think that the problem is much less for other drugs than, you know, I see the problem with this consistency that we need with phenytoin.

Q. Can I just clarify that, Professor Sander? I think what you have just explained is this consistency of supply which MHRA were concerned about, there were two reasons why the guidance was issued: one was the psychological concern, but two, also clinical risk. Is it both or is it more one?

A. I think that it differed for different drugs. It is a very common thing that people come to the clinic and they have no idea which drug they are taking.

People will say: oh, I take two pink or two blues and one orangey, one brown. Some people will come and say: I take 12 tablets. You know, it is just a unit, and you do not know. Of course you have the medical records, you will know, but people -- a lot of people with epilepsy have cognitive problems and you can see

this happening.

One thing that makes -- it is really the problem that came in with the parallel imports was that people did not like, you know, this lack of consistency. In a case -- a good example, was lamotrigine, Professor Walker mentioned yesterday. Lamotrigine was done -- was fabricated -- Glaxo Wellcome at the time, made this drug in a place called Runcorn. It was then distributed throughout Europe, would be locally packaged and would then be imported to the UK because -- from Portugal, because in Portugal the reimbursement was 30%, so there was a 70% difference. So almost all the lamotrigine, Lamictal, at the time, that was here, came from Portugal, and people really did not like the Portuguese packaging, the insert in English, and this is where the psychological thing comes in, and we have seen this with other drugs.

I think that consistency of supply I always write to -- almost every time I write to primary care saying: for this person, with this chronic condition, it is very important to keep consistency, because people, you know, they do not like a break of routine, having different colours or different shapes of tablets.

PROFESSOR WATERSON: Just to check, in this case, of a parallel import, lamotrigine, the other problem that

you mentioned would not exist in the sense that it was all produced by the same factory.

A. Yes, but --

PROFESSOR WATERSON: So it was just a psychological problem?

A. Yes, exactly, and this point was clearly psychological, and in my little sort of things, the ones that really irritated people even more than the Portuguese was the Greek, and there was a time that we were getting Greek topiramate, which is not a great drug, but that is another issue, but it came, because it was cheaper in Greece, so we got a lot of topiramate with Greek packaging, and again, this was actually manufactured in the same place, but it was packaged in a different way with a different insert, sometimes even the commercial name was slightly different, and that was not very clear when people could see the Greek package.

So I have no doubts that for some people the consistency of supply is psychological, because, you know, you could try to convince them: this is all the same, it is just it came from this place, but you were not always convinced that the person was happy with your disclaimers.

The other thing that would then happen is if a seizure would happen, it would be blamed on this: oh, I was taking the Portuguese, it must be not as good as

the British one, but it is the same. So in that sort of case I would say psychological issues do play a part.

MS MORRISON: In a case of phenytoin, though, is it clinical or is it psychological?

A. I think that we tend to tell -- I tell people that I look after if they are taking a drug they should always try to get the same. I do not remember what I did when phenytoin was a mainstay of treatment, and it was when I started as a consultant quite a long time ago. I do not remember what I would say, but nowadays if someone -- I would write to say that consistency is important in the case phenytoin more than other drugs because of this difference potential bioavailability from one formulation or one generic to the other.

MS MORRISON: Sir, those are all of my questions. If the Tribunal has more questions?

THE PRESIDENT: Thank you very much, Ms Morrison.

Do you have the MHRA guidance in front of you, Professor? Do you have this document, the MHRA guidance in front of you?

MS MORRISON: I can give the reference for Opus if that would help.

THE PRESIDENT: It would be helpful if we could bring it up.

MS MORRISON: It should be at {XG/307}.

THE PRESIDENT: It will come up on your screen, Professor.

There we are.

A. Yes, I can read it now, thank you.

THE PRESIDENT: So first of all, you are familiar with this document, I take it?

A. Yes.

THE PRESIDENT: Can I ask you just a very general question, before we go to the specifics.

Do you agree with it? Do you think it is right?

A. I have my views. I think that for the reasons that we discussed for quite a lot of people with epilepsy, consistency is something that seems to count. I think that in practice this is not taking much into account. You know, as I said, we write to primary care saying they should stick to this and you get a patient because when they went to see the drugstore or the pharmacy or the chemist, they did not have that one; rather than wait for next week they were given something else.

So in practice, I am not quite sure if it operates in a good way. I have not seen any major disasters in a sort of consistent way as a result of that.

So, yes, it is a good intention. I think that there is no doubt that something should be there, but if that would make a big difference, if everything was equal, I would say that the only time that it will make a difference will be the one in category 1, particularly

with phenytoin.

THE PRESIDENT: You see, having listened very carefully to your earlier evidence, I was expecting you to say that you were not very happy with this document. No, no, let me unpack, because I am wondering how far my expectation that you would disagree was based upon a misunderstanding that I have about this document, and so if you do not mind, I will unpack that, and you can just see how far I have misunderstood.

There are two types of change of treatment that a diagnosed epileptic might undergo. You could have the change to a new regimen, change to a new regime, in other words, someone has been on phenytoin for 30 years, they are getting a little bit cross about the double vision, and they say: look, I would like to change, and you have a whole range of drugs which you can deploy. Of course, you explain it to the patient and the patient consents (inaudible) to what you have said, but you would be quite keen, I think, to effect a change from a phenytoin regime to something else?

A. As it would be if this was carbamazepine, if it was --

THE PRESIDENT: No, no, of course. I appreciate that your concerns are broader and relate to the question of enzyme inducers, but, forgive me, we are really just interested in phenytoin.

A. Yes.

THE PRESIDENT: But obviously if you need to answer more widely, that is fine. Do you consider that this document says anything at all about the changing to a new regime? No?

A. No.

THE PRESIDENT: That is because it is referring to changing products, not changing regimes?

A. Correct.

THE PRESIDENT: So the value of this guidance is the second type of change that I was going to articulate, not a change to a new regime, but a change within an existing regime, in other words, you are staying on phenytoin and, in those circumstances, there are two issues which arise specifically in relation to phenytoin, or one specifically in relation to phenytoin, one generally. The general one is the psychological concern that a patient may have, and I am sure it varies, to stick to the same regime as worked in the past, in other words, it is your coloured pills point.

A. Yes.

THE PRESIDENT: Yes. That concern would probably be as great if phenytoin pills were repackaged into something different than if they were something different altogether. You are nodding?

A. Yes.

THE PRESIDENT: The other concern regarding an intra-regime change, a change within a regime, is that because there is a sensitivity to the composition of the product, particularly in the case of phenytoin. You need to be very careful when you substitute for a phenytoin product produced, let us say, branded, for a generic which is intended to be the same but because it may not be, will have adverse or potentially adverse clinical consequences?

A. That is correct, yes. I think that this is a switching from -- either from the brand to a generic and generic back to the brand, and then to another generic. With phenytoin, it does carry a risk, particularly if the person is very near the saturation point, so that could go one way. So it is important that -- this is really the one concern I would have in terms of this guideline or whatever it is called, it is with category 1, and within category 1 is phenytoin the one that I would be more worried about than others.

THE PRESIDENT: More worried about changing from generic to branded or branded to generic, that is where your concern is localised?

A. Yes, it is changing to another preparation within that same so the --

THE PRESIDENT: I see.

A. But this often goes without any problems because we do not even know it happened until the person comes and shows you they have a different thing. So that is the reality.

THE PRESIDENT: That is very helpful, Professor, but just to nail the ambiguity in my mind: you do not regard this document as in any way cramping your style, if I can be colloquial, in terms of change of regime, in terms of moving either to or indeed from phenytoin. That is not what this is getting at?

A. Yes, I would easily go to desert island without taking this document.

THE PRESIDENT: I think that is enough of an answer for my purpose, but thank you very much.

MS MORRISON: Sir, obviously if you have any questions at any other point, Professor Sander will be questioned later, but shall we move then to Professor Walker's --

THE PRESIDENT: Yes, indeed --

PROFESSOR WATERSON: Could I?

THE PRESIDENT: No, of course, Professor.

PROFESSOR WATERSON: When you were talking about, early on you said initially or earlier you saw 10% to 12% of people on phenytoin, and now that has gone down to less than 3%.

A. I can tell you for sure that I am quite confident in the last number, about the current. I would not be able to exactly put, but we have seen a dramatic -- when I started my career, phenytoin was the mainstay with phenobarbital and carbamazepine. This was a time we had four or five drugs. Nowadays we have well over 25 drugs. So that is the case.

PROFESSOR WATERSON: But in fact we know from the statistics that that has been a gradual decline in the use of phenytoin, so the inference I draw from that is that the people who are on phenytoin are largely legacy patients who find phenytoin perfectly acceptable for whatever reason, or they are risk-averse or whatever, so these are legacy patients who continue on the product. You tend to see the problem patients rather than legacy patients?

A. That is correct, and I think it is fair to say that they are legacy patients. Most of the time, they are quite happy, they do not come to the hospital because all is hunky-dory. You could even argue that many of them should be off drugs. However, once you have been seizure-free and you are driving, for instance, you would have to stop someone driving -- well, you would have to advise them to stop driving when you want to take a drug off, and that is what makes a lot of people

to decide to stay on the drug treatment.

So I would say that with the 600,000 people with epilepsy in the UK, if we could easily take them off drugs without stopping them driving, probably the numbers would go down quite dramatically, because the majority of people with epilepsy, they are seizure-free, and the only reason they are labelled as a person with epilepsy is because of the drug they are taking. So I think that that is something that I -- it is important that we remember.

PROFESSOR WATERSON: Yes. Thank you.

MR DORAN: Just to pick up on that point, Professor, so the particular reason that you have for that, for wanting to take them off the drug in such a case, is because of the enzyme-inducing effect of, say, phenytoin or the potential for interactions with other drugs.

A. I think that if there is any sign of something not being right, and I have heard this story so many times, I feel so much better now that I am off the drug, and I think that the main driver would be to avoid problems.

Having said that, I know of one retired physician who was diagnosed phenytoin in the 1950s, and he is now in his 90s, he is on a low dose, but he has had no problems with his phenytoin, and, you know, when I told him about -- we were laughing, because he said,

you know, I got so -- I am not saying that this will happen to everyone, but the risk is higher with this category of drugs than with other drugs, and I also take the point that was made already that we might not know the full picture of side effects of some of the newer drugs. However, I think that the mechanism of pharmacovigilance that we have nowadays are that we are really picking up problems quick, and in my life as a consultant we have seen four drugs been withdrawn due to side effects, so that is something that we need to also remember, that we need to always keep our eyes and ears open to potential problems.

MR DORAN: Thank you.

THE PRESIDENT: So Ms Morrison, you have no further questions for the teach-in?

MS MORRISON: Sir, thank you, we will move then to the cross-examination of Professor Walker, or would you prefer to take the break now?

THE PRESIDENT: I think we will take a break, but, Professor, thank you very much. You will be coming back to be cross-examined, so you will get more questions from other barristers, but at the moment, thank you very much for your time, we greatly appreciate your help, and do, please, take a seat back in the rows behind counsel.

We will rise for ten minutes and we are ahead of

time, so I think we can --

MS MORRISON: I just want to say, sir, thank you for the panel taking such time with the teach-ins. I know we actually only scheduled 20 minutes each, but I think they are probably the most useful part of this evidence, or half an hour each, so I just want to say thank you very much for taking the time for the teach-ins.

THE PRESIDENT: No, I do not think any thanks were due, we have benefited considerably from both Professor Walker yesterday and Professor Sander today, so thanks are due to you for so carefully helping us both. Thank you very much. We will rise for ten minutes.

(11.14 am)

(A short break)

(11.31 am)

MS MORRISON: Professor Walker will be joining us.

MR JOHNSTON: I was expecting you to call Professor Walker again.

THE PRESIDENT: He is on his way.

MS MORRISON: I think, sir, we agreed that we could just go back into being sworn without having to go through all the mechanics again.

THE PRESIDENT: I will explain the position to the witness when he is...

PROFESSOR MATTHEW WALKER (recalled)

THE PRESIDENT: Professor, welcome. Do sit down, we are not going to re-swear you. I regard you as still under oath and we do not need to bother with that again. Can you just make sure you have the necessary documents you need.

THE WITNESS: Yes, thank you, sir.

Cross-examination by MS MORRISON

MS MORRISON: Professor, there should be a bundle in front of you that is the expert reports in this bracket, so it would be XE4. I do not know what the second file is. There should also be a bundle with position papers in that it might be handy for you to have. That will be XE6. I do not know if that is the other one in front of you, I do not think it is, it might be on the shelves behind you?

A. Yes, my position paper I think is behind my ...

THE PRESIDENT: Perhaps someone could assist with the Professor just to make sure he has the right files.

A. Yes. I have my papers and position papers.

THE PRESIDENT: That is good.

MS MORRISON: I am hoping for the most part we will be able to just do it on the screen in front of you, but if at any point you want to look and contextualise the passage I am taking you to, please just do. I am sorry, sir.

THE PRESIDENT: Not at all. Professor, I was going to say we are going to go straight into cross-examination, that is to say counsel for the CMA will be asking you questions. You will not have any further questions from Mr Johnston until re-examination. That is because we got all that over with yesterday, so that is how it is working, but I am sure Ms Kerr Morrison will bowl you a few easy balls just so you can get your sight in.

MS MORRISON: Get your sea legs.

THE PRESIDENT: So over to you, Ms Kerr Morrison.

MS MORRISON: I wanted to say obviously if the panel have any questions at any point, please just indicated, I will not be troubled by that.

Professor Walker, I understand that you are a consultant neurologist at the National Hospital for Neurology and Neurosurgery and you are a professor of clinical neurology at the Department of Clinical & Experimental Neurology at UCL Institute of Neurology University College London; that is correct?

A. That is correct.

Q. Professor Sander is also a consultant neurologist at the National Hospital for Neurology and Neurosurgery?

A. He is, yes.

Q. And Professor Sander is the current head of the Department of Clinical & Experimental Epilepsy at the

UCL Institute of Neurology?

A. Yes, and I was the prior head.

Q. You were the prior head?

A. Yes.

Q. So you work together?

A. Yes.

Q. You have also worked together on a number of publications, I understand, from your CV?

A. We have, yes.

Q. Each of you have many years of specialist experience?

A. We do, yes.

Q. So I think -- I think you have said this expressly yesterday, Professor Walker, that you respect each other's clinical expertise?

A. I hope so, yes, certainly from my point of view, and I hope from his.

Q. You covered your five reports yesterday with Mr Johnston and the Tribunal. You have been very busy in this case, there is a lot of material from you, but can I also just check, you gave live evidence at the previous hearing; are you happy that that evidence remains accurate and reflects your opinions on phenytoin in this case?

A. I am, yes.

Q. Despite what might appear to be the case, I believe there is actually quite a bit of common ground on the

clinical evidence issue, so in my questions today I am going to try to clarify the common ground and ask some questions that sort of follow-up and address the issues that there seem to be some differences on, but the first topic is very easy, this is the sea legs topic, but my first topic is in regard to the balance to be struck in prescribing anti-competitive seizure medications.

So can you just tell me for starting off whether or not you agree with these what I understand to be very basic propositions. The first one is there is always a balance to be struck between finding an effective treatment for a condition like epilepsy and the side effects that that treatment may cause?

A. There is always a balance to be struck, yes.

Q. So you do a risk benefit analysis every time, every time you are deciding what therapy to give a patient?

A. I do, yes.

Q. And whether or not the side effects are worth it is really a question for the patient with advice from their doctor?

A. It is, yes.

Q. Presumably your patients, like those of Professor Sander, want to achieve seizure-freedom while suffering as few side effects as possible?

A. That would be the ideal, yes.

Q. Indeed, they would probably like to achieve seizure-freedom without any adverse effects in the ideal world?
A. Yes, in the ideal world they would like seizure-freedom, no side effects, a drug that they take just once a day, there is a whole host of things that they would like, yes.
Q. We would all love it. You used a lovely phrase yesterday, you said you need to take the patient in front of you in assessing what the right drugs might be, so you need to kind of look at the individual's very particular individual circumstances in deciding what they can tolerate as compared to a different patient?
A. That is correct, yes.
Q. Alongside considering the drug's side effects, the doctor will also consider, for example, how easy it is to use the drug?
A. That is absolutely correct, yes.
Q. So that would be interactions with other drugs?
A. That would be interactions with other drugs, the pharmacokinetics and I think we have spoken about this, the phenytoin has unusual pharmacokinetics.
Q. So my second topic, Professor Walker, is the usage of phenytoin and how things have changed over time, and you have quite helpfully given some numbers at various

points, but could we just first go to paragraph 1.2 of your position paper which is at {XE6/2/1}.

A. Yes, I have that here.

Q. I think it will appear for everyone else. So in that paragraph you say, of course:

"The main aim of epilepsy treatment with antiseizure medication is to stop the seizures or at the very least to reduce seizure frequency and severity. A further aim [as we have just been discussing] is to accomplish this with the fewest adverse effects from medication."

Then you say:

"For many people, phenytoin remains the treatment that achieves this, even when other medications have failed or have not been tolerated."

I just wanted to discuss first that phrase of "many people". Do you think that is accurate in terms of how many people are using phenytoin today?

A. I think there are many people using phenytoin today where that has been achieved, yes, and certainly that has been my experience.

Q. So could we just look at some numbers. I understand from your first report that back in 1993, phenytoin was the most prescribed AED in the UK at almost 40% of patients. That is right, is it not?

A. Yes, that is correct.

Q. But by 2008, the percentage had declined to 18%?
A. That is correct.
Q. So before the 2012 to 2016 period that we are looking at, usage of phenytoin had already more than halved?
A. Yes.
Q. And it has continued to decline?
A. It has continued to decline, yes.
Q. We do not actually have precise statistics for the 2012 to 2016 period, so I am going to ask you so help me in trying to figure some out and see what we can do.
I understand that in 2012, or going into 2012, there were about 600,000 people in the UK with a diagnosis of epilepsy who were prescribed --
A. That sounds right.
Q. -- does that sound right to you? In fact, the document I had on this was a Joint Epilepsy Council document and you mentioned yesterday that you were the chair, so you would be very well aware of this.
Now, if we can go to the Decision at paragraph 2.123, which is at {A1/1/57} --
A. Sorry, this is where, please?
Q. It will come up on the screen in front of you, Professor Walker, do not worry. What that paragraph basically explains is that, the second sentence of paragraph 2.123:

"During the Relevant Period, the estimated number of patients taking phenytoin sodium capsules fell from 57,500 [in] (2012) to 45,000 [in] (2016) ..."

So I am going to give you some rough maths based on that. My understanding is that in 2012 there was roughly just under 10% of patients would be taking phenytoin capsules at that time. Does that accord with your recollection of your own practice at that time?

A. That would probably be about correct, yes.

Q. If the 600,000-ish holds good, it would be about 7.5% by the end of the relevant period?

A. Yes.

Q. These figures would include what the CMA has been referring to as legacy or existing patients?

A. They would do, yes.

Q. Can we go to paragraph 5.2 of your first report which is at -- sorry, I have not given the Opus reference -- {XE4/1/8}. Now in the first sentence of that paragraph you explain -- you put the point about phenytoin use having declined. Then you say:

"By 2008..."

And you make the 18% point, and you say:

"... my experience now is that only 5-10% of my patient population remain on phenytoin."

That report was dated February 2017, so by just

after the relevant period we are down to somewhere between 5% and 10%?

A. Yes.

Q. That of course again would include legacy patients?

A. That would include legacy patients.

Q. Do you have any sense of at that time what proportion of those patients would have been legacy patients in comparison to patients who are being newly prescribed phenytoin as a third-line drug?

A. Of my own practice?

Q. Of your own practice.

A. I would think the -- well, the majority would have been legacy patients, but against that some of those would have been started on phenytoin as a sort of new prescription prior to that year. I would say that the minority, I could not give you precise figures, but the vast minority would be patients in that particular time period that have been started on it anew.

Q. So by your fourth report in 2022 you said that approximately 5% of your patient base were taking phenytoin. Would that be right?

A. That would be about correct, yes.

Q. Then in your position paper from just a few months ago, you say that the figure is now about 3% out of over 1,000 patients?

A. That is correct.
Q. That is about 30-ish patients. Has the percentage dropped in a year? Is it that you have changed patients off of phenytoin or they have stopped treatment? How did it go down?
A. There are two things that occur, one of which is my patient population has a turnover, so both unfortunately patients die, as we all do, so there is a group of patients who drop off in that way, there is a group of patients who are stable who get referred back to their physicians, and then there will be some patients whom I will have taken off phenytoin at that time as well, yes.
Q. That is very helpful, thank you, Professor Walker.
How many of these patients, the 3%, would be legacy patients?
A. The majority of those would have been legacy patients, so I would say that overall my prescriptions for phenytoin would probably be somewhere around about two or three per year. I think, you know, we have to take this in context as well. I mean, I think Professor Sander mentioned that over the last year eleven patients had been started out of 9,000. The majority of patients do not have their drugs changed at all, or they have the drugs that they are on, the dose

is adjusted. So in fact, if I can refer back to a paper in which he was an author, when we looked at the total number of patients which had drug changes within our population over a year, that would have been about -- probably about 200 or 300. So about say, 200, well, 200 or 300 would have changes in that particular year.

So when you say eleven people were started anew or afresh, that is actually quite a large number, and if you look in the ranks of drugs that we use, there is a whole host of, for example, the third-line drug treatments that I expect you would find that, no, no one was started on, so I would be surprised if tiagabine was started on anyone, I would expect gabapentin was many fewer patients. So it is there at about halfway. There are drugs that are used much more, and especially when new drugs come along.

So when a new drug comes along, a large number of people would be put on that drug, they have never tried it before, whilst many people have tried phenytoin before, so again, it restricts what you can use.

So we go through all the drugs that people have tried when they are referred into us, many of them have already tried phenytoin, and so you would not then say: right, let us try it again, if it had failed in the past.

Q. Can you give me an idea of how many patients come into the service on a yearly basis?
A. It is the whole service.
Q. Yes.
A. I can try and estimate that. It is about, say -- it would be about 20%, it would be about a fifth, maybe about 1,000 to 2,000 new patients, maybe a little bit -- yes, somewhere around that.
Q. It is just that eleven seems like a small number compared to the number of patients that would be coming in?
A. So a large number of those will not have drug changes and as I say, overall, when you look at the -- the number of patients in our service has not change dramatically over the last 10, 15 years, and when we look back to the study where they looked at the total number of drug changes over a year then, it was about -- it was 400 over two years, so it was about 200 per year.

We probably have slightly more now, and when a new drug comes along, so cenobamate has just come along and cenobamate is probably about 600 or 700 prescriptions in the last year because it is a new drug and we would just use that. When you look overall at the number of drug changes that we are doing, actually it is not that -- I mean, it depends on how you look at it but it is not

that small, and when you compare it to the total number of drugs which has already been said, there are 25 drugs, and if you expected each of those drugs to take an equal proportion, then you would expect about each one to have about 10 per year, so it would look similar to many of the other drugs that we are using.

Q. But only three of 19 consultants have prescribed phenytoin in that last year, so does that not suggest to you that maybe a number of other consultants in the service share Professor Sander's views of phenytoin?

A. Sorry, maybe I misheard, but I heard that Professor Sander was one of those consultants as well, as he had said he had started somebody on phenytoin in the last year. I am not sure who those three consultants are, and the other thing that has happened, again, which may reflect numbers, is that certainly over Covid the prescriptions for phenytoin in my practice were fewer because it was difficult to get monitoring, so we started -- I probably started fewer people than I would have done before. I do not know over the last year whether that is the case or not, and I would need to see the data so I cannot really address that.

Q. So you have not seen the data?

A. I have not seen those data, no, no, so that was completely new to me, the data that was presented there.

Q. Could we go to {XF4/7/1}, please. It will come up on your screen, Professor.
A. Oh, right, thank you very much. Oh right, okay, yes.
Q. I wonder if you could just read the abstract paragraph, if everyone could read that. (Pause)
A. So:
"Phenobarbital and phenytoin ..."
THE PRESIDENT: Just read it to yourself, Professor.
A. Oh, to myself, okay.
THE PRESIDENT: We will all read it, and then there will be some questions.
(Pause)
A. Yes, sorry, can you just go up a bit so I can just have the --
MS MORRISON: Yes, of course, if you see the top of the page.
A. The top of the page, just the --
Q. It is a paper from 1983.
A. 1983, yes, okay.
Q. So my simple question, Professor Walker, is it says at the end of that paragraph having outlined the side effects of phenobarbital and phenytoin that:
"Many experts avoid the long-term use of phenytoin because of its insidious and potentially dangerous side effects."

Would you agree that many experts would avoid phenytoin for those reasons?

A. So it is true that experts will avoid it because of the side effects that it can have. In 1983 things were slightly different and prior to 1983, to put it in into context, were different from later. So there was widespread, certainly from the 1980s, there was then widespread use of drug level testing, and so prior to that, drug level testing was not so avidly done, in fact, it really only started full scale in the mid-1970s, and so there had been a group of patients who had been on phenytoin for large amounts of time with very high levels, who may well have had toxicity.

I think that changed, really, from about the 1980s onwards, when -- well, from the early 1980s onwards with more widespread drug testing.

I think they also point out -- I do not have the whole paper there in front of me, this is a review, that the neurotoxic effects particularly in people -- children with epilepsy with severe brain damage, it is not a group of people that I treat, but it may be specific groups of people where you may want to avoid phenytoin.

Q. You mentioned, though, in your answer earlier that normally -- you have had a new drug in the last year and

there will be lots of people tried on the new drug?

A. That's right.

Q. Your practice really though is to use the newer drugs wherever you can do so?

A. No, so the practice would be that we would -- many of the patients have already tried phenytoin, so I think it is a bit more nuanced than that. When a new drug comes along, the patients will not have tried that new drug, and so then there is much more widespread use of that new drug, and so the use of the new drug is partly because it is new and people have not been exposed to it.

Q. Thinking back to the numbers that we have been looking at, just pulling the strands together, I think it is fairly reflected in your evidence already, but just to confirm, the use of phenytoin capsules has long been in decline?

A. It has been in decline, yes.

Q. From 2012 onwards, the percentage of patients taking phenytoin capsules has been around 10% or below?

A. It has, yes.

Q. So I just wanted to go back to that reference to "many people". You know, it is a small number of cases that are using phenytoin capsules out of the whole now?

A. It is a small percentage. It is still many people.

I still see many people on phenytoin.

Q. Do you have any reason to dispute Professor Sander's figure that it would be less than 3% of the ASM prescriptions in England in 2022?

A. I have no reason to.

Q. I now want to move on to consider the reasons for the decline in use of phenytoin and I think you have already explained this, but just to go over it, I think three of the main reasons are: first, it is non-linear pharmacokinetics; second, the way it which it interacts with other drugs and third, its narrow therapeutic index?

A. Yes, those would be my main reasons why it has declined in use.

Q. I wanted to first discuss the issue that phenytoin has non-linear pharmacokinetics. I know we have discussed this a few times, but I do not know if it would assist the Tribunal for Professor Walker to explain it again or you are happy?

THE PRESIDENT: Well, I do not think there is any harm in repetition. I know that you will not unduly repeat, and I will stop you if we are not getting any benefit from it, but I would not overcut your cross-examination notes simply because you are concerned that you may be treading ground again. These are nuanced questions.

MS MORRISON: I just know, sir, that I had to hear it quite a few times before I got the hang of it, so I thought it would be good to kind of go over and you can let me know if I am preaching to the choir.

THE PRESIDENT: I think that is a perfectly sound instinct.

MS MORRISON: For many drugs the plasma concentration of the drug is proportional to the dose, is that right?

A. That is correct, yes.

Q. But with phenytoin this is only the case low subtherapeutic plasma concentrations.

A. Yes, so can I just add to that actually?

Q. Of course.

A. So there is a therapeutic range for phenytoin, and that is determined by a large population of people, and determining whether those people have side effects or whether they have efficacy, and the range would be where the majority of people stand in terms of having few side effects or no side effects and efficacy.

There are a substantial number of people who can have subtherapeutic phenytoin levels, and they may well still have efficacy, and indeed, I have a number of patients who have exactly that, and there was a very nice study which -- because, again, for a long while, sir, there was an idea that we should be treating the blood levels and not the person, and so people would

say: oh, the phenytoin level or whatever drug level was below this, we need to get them into the therapeutic range, and that, thankfully, I hope, has gone completely, because what we have discovered is that some people can tolerate much higher levels, and so can be beyond the therapeutic range, and some people can gather very good control with lower levels, and if you try and increase the number of -- the drug levels, increase the dose, all you do is give them side effects rather than improve their long-term outcome.

Q. Just to then build on, the point with phenytoin is that at higher concentrations the ability of the body to break down becomes saturated so that small increases in dose can result in large increases in plasma concentrations?

A. That is correct, that is what non-linear pharmacokinetics --

Q. So essentially the blood levels are not proportional to dose, but this means that small increases in dose can result in someone from going from lower, moderate blood levels to very high blood levels leading to side effects?

A. That is absolutely correct.

Q. So non-linear kinetics can make it very difficult for practitioners to regulate the dose?

A. It can make it difficult to regulate the dose, and does mean that we have to try to keep an eye on drug levels and the recommendation would be to get regular drug levels of the phenytoin.
Q. We will come back to those blood levels shortly, but just to confirm, then, this difficulty is then compounded by the fact that phenytoin interacts with other drugs?
A. Yes, it interacts in two ways, so it induces the enzymes, it is an enzyme inducer, as we have heard, and so that will increase the breakdown of some drugs, and not all drugs, and it can also, because it is metabolised by the liver it can also be subject to interactions the other way where other drugs can affect its levels, usually by decreasing them.
Q. So one of the issues is then that it can interact with the other anti-seizure medications that it is being put as a third-line drug alongside of?
A. Yes, it can.
Q. So it can vary the levels of the other anti-epileptic drug?
A. Yes, and that is unfortunately a quality that is shared by many of the anti-seizure medications that we use, and that is what makes quite a lot of our job quite challenging, is that when we are adding in medications,

we may have to adjust the other medications as we add them in. So if we take cenobamate, which is the newest drug and which we -- I say we have probably had 700 or 800 prescriptions, I am sure Professor Sander will be able to tell me the exact number, that has quite significant interactions that makes its use again difficult, but we do -- we cope with that by adjusting the levels of the other drugs when we introduce it.

Q. But in principle that is one of the other reasons why phenytoin is very difficult to use, is because of these interactions?

A. So the interactions make it difficult to use as does its non-linear pharmacokinetics.

Q. Another reason, another way it interacts is, I think you have mentioned this just now, that it is a potent enhancer of drug metabolism, which means this breakdown of drugs by the liver, that is right, is it not?

A. That is correct, yes.

Q. So the consequence of this is that the serum level of other drugs can fail when phenytoin is used alongside them?

A. So they can become lower when you use phenytoin alongside them, yes.

Q. So that is the physiological issue arising, that when you add phenytoin, it can also make it very difficult to

use?

A. Yes, so as an enzyme inducer when you are adding in phenytoin it can make it more difficult to use because you have to be wary of the effects it can have on the other medications that somebody is taking.

Q. Then a further issue and difficulty on top of that is there is marked variability between people in their efficiency in metabolising phenytoin. I have given myself some tongue twisters today. I will say that again, these difficulties are then compounded again by the marked variability between people in their efficiency in metabolising phenytoin?

A. Yes, so people who break down phenytoin fall into two big groups: those who are fast metabolisers and those who are slow metabolisers and they will need different phenytoin doses, so that is correct, yes.

Q. There is also an issue of people having a variable absorption of phenytoin?

A. So the variable absorption is -- tends to be more related to people who are taking it alongside antacids, so we would recommend people not taking it with antacids. There is an issue as well about whether people are taking it with food or not with food, so we tend to recommend that people take it the same time of day, and take it probably without food. That is

certainly my recommendation. These are qualities that are shared by many of the medications that we use.

Q. Focusing on phenytoin, these difficulties are important because it has a narrow therapeutic index?

A. That is correct.

Q. Just to confirm that that means there is a relatively small difference between the level of the drug that is necessary to achieve therapeutic efficiency and the level which if exceeded might result in adverse effects?

A. That is correct.

Q. What all this means in basic terms is that it can be difficult for practitioners to get the dose right?

A. Yes, it can be difficult, and it can be difficult to use, which is why I feel it has largely become a third-line drug. So it remains efficacious, the side effects can be managed, because you can reduce the dose. When starting somebody on it, you need to monitor the drug levels, so again, that is a complication. So these factors have meant that it has moved down the order, and to my mind is probably the main reason why it is not used as much as it was used previously.

Q. It is also one of the reasons why, if someone is going to be prescribed phenytoin, they are usually referred to a specialist clinic like that to which you and Professor Sander work at?

A. Yes, so when you say specialist, yes, so they will often be referred to a tertiary referral centre which is a centre which has expertise in managing people with refractory epilepsy. In fact, the NICE guidelines state that anybody who has failed two anti-seizure medications, regardless of what they are, should be referred to a tertiary referral centre, and so the ideal is that all people who have complex epilepsy should be seen by us, and sadly that is not the case.

Q. The difficulties that we have just been talking about are also why phenytoin is only used in a very limited number of cases now.

A. They are the reason why it has become third-line treatment, that is correct.

Q. The vast majority of cases that phenytoin will now be used in are legacy cases rather than wholly new prescriptions?

A. Yes, so the majority of people in whom phenytoin remains to be used are people in whom phenytoin is still being there, and people take different views or attitudes to this, and many of the patients we see, for example, are not seizure-free, and as Professor Sander said, you would be a brave person to take somebody who is seizure-free off their medication if they have no reported side effects, but when people are not

seizure-free, and they are on medications, then we do not like people to be on more than about two or three medications, and so we cannot just add in medication after medication until they are on 20 medications, so you try and remove one and add in another. So the legacy patients that we have who are legacy patients on phenytoin are usually patients in whom people have tried to withdraw phenytoin and have failed, because it has been necessary to maintain at least some seizure control, and certainly that has been my experience.

So I think two of the cases that I gave as examples, the phenytoin was necessary because people had tried to reduce or withdraw the phenytoin, and that had had devastating consequences. In fact one of the patients, people -- somebody had tried to reduce the phenytoin and the person ended up with very prolonged seizures and ended up admitted to hospital because of it.

So when we say legacy, certainly in our practice, as Professor Sander says, very often you would try and get people on to medications that may have fewer side effects, you may try to get people on to medications that are easier to use. If you wanted to try a new medication because they are not seizure-free you would have to withdraw their medication, and which medication you withdraw is again personal choice, there is

unfortunately no good guidance, and so many of the patients who are legacy patients that we see, somebody has tried in the past to withdraw their phenytoin and failed.

Q. Just to clarify, though, your position is also that phenytoin should not normally be used for people with newly diagnosed epilepsy?

A. That is correct, and I think there is no disagreement between Professor Sander and myself on that point, that there are now good and big trials of medications who -- when people have been newly diagnosed, and lamotrigine, levetiracetam would be the drugs that I would also take to my desert island.

Q. It is lovely to have some agreement as always. Moving on, then, I would like to now move to discuss how phenytoin compares to other ASMs in respect of these issues. I think this flows from the discussion we have had already, but just to confirm a few points.

So am I right in saying that phenytoin is the only common ASM that has both a narrow therapeutic index and non-linear kinetics?

A. Yes, it is, as commonly used, yes, absolutely.

Q. I think you have actually identified one other drug -- gosh, it is stiripentol --

A. Stiripentol, yes, that is used a lot.

Q. That is used for Dravet Syndrome; could you explain what that is?
A. Yes, it is used specifically in children with Dravet Syndrome.
Q. Phenytoin is the only ASM that requires blood level monitoring to aid dose adjustments?
A. It would be the only one that I would recommend to have blood level monitoring for that reason.
Q. We have discussed the difficulties in using phenytoin, but just to confirm your evidence in writing has been, in your fourth report, the difficulties using phenytoin which we have been discussing are generally dealt with by blood level monitoring via primary care support.
A. That is correct.
Q. And in your fifth report you say that acute side effects can be readily resolved and in most cases reversed by adjusting the dose of phenytoin?
A. That is correct.
Q. You basically say it rarely causes real practical difficulties.

Professor Sander said though, focusing on the acute side effects, Professor Sander says: look, they are not readily resolved because of the drug's non-linear kinetics which means that even a tiny alteration in the dose of phenytoin may lead to dramatic changes in

toxicity or lack of effect. Do you reject that? Do you maintain it is easy to readily resolve the difficulties?

A. It is easy to readily resolve the difficulties, and this is true -- so there is a group of drugs which are called sodium channel blockers and they are probably amongst the most effective drugs that we have in epilepsy, so they include lamotrigine, which is first-line, carbamazepine, phenytoin, oxcarbazepine, there is a whole range of -- lacosamide, there is a whole range of those drugs, and they all have exactly the same dose-related side effects which is that as you push the dose up, they affect the cerebellum, which is the back of the brain that maintains balance, and so people get loss of balance, they get double vision, they feel sick, and very unwell, and all these drugs have those particular side effects.

For most of those drugs, in people with refractory epilepsy, what we would do and what we would tend to do is we would tend to build up the dose slowly, and if they start to exhibit those side effects, so they start to become unsteady or have double vision, we then reduce the dose and phenytoin is no different in that respect, we would start somebody on phenytoin, would you gradually build up the dose of phenytoin, and then you would reduce it if they were to exhibit those effects.

With phenytoin, we are more cautious in building up because, as you rightly said, we get non-linear pharmacokinetics so that suddenly there may be a jump in levels and there are a number of ways in which we can adjust the dose, so, for example, 25mg is the smallest capsule, I have people who take 25mg alternate days in order to try and adjust the dose in that way, and phenytoin has a reasonably long half-life, so it hangs around long enough that you can even do that, you can have alternate day doses.

So these side effects are usually quite easily managed. I think that is generally borne out by, for example, the large randomised control studies back in the 1980s, the paper from Mattson that is there in my evidence, where they randomise people to carbamazepine, phenytoin, phenobarbital and primidone, and overall carbamazepine and phenytoin were much better tolerated than the others, and again, as I say, that is because you can just adjust the doses and those two drugs work in very similar ways.

Q. I think, though, in terms of any agreement with Professor Sander, you agree that you have to carefully manage the use of phenytoin?

A. I think there is absolutely -- I think Professor Sander and I in fact agree on many things --

Q. Yes.
A. -- not surprisingly, and I think we both agree that you have to be careful with phenytoin and that it is a drug with, as you say, a commonly used drug with unique pharmacokinetics.
Q. Perhaps, not to make you blush, but perhaps it is your expertise that makes it more easy for you to manage than, say, a GP or a nurse in the primary care context?
A. Yes, so similar to Professor Sander, my expertise is almost exclusively epilepsy, I see a similar number of patients, have a similar number of patients per week, so we have similar practices, we see a large number of people with epilepsy, and we -- so we deal with these issues on a day-to-day basis.
Q. Professor Sander says that in his experience, getting primary care physicians to make adjustments in times of clinical need is not easy and that this was the case in 2012 to 2016. Did you just have a very different experience?
A. So in terms of getting -- so with phenytoin, I did not have particular difficulties. I mean, as all things, I think it varies on GP practices. So things have become more difficult more recently, and that is, I think, because of the increased workload of GPs. Back then, there would be GPs, I have one who I can think of,

straight off the top of my head, with whom I have a patient on phenytoin and the GP works very closely with me and will send me the drug levels and I will write back and ask them to adjust if necessary.

So provided you can get a good relationship with the GP, and if you are willing to put the effort in, then you can adjust the medications in that way. We are getting to a stage now where GPs are -- again, I cannot speak for GPs, but I think under the pressures they are under, they are finding it very difficult to manage anything, and so I think things are different in that respect, but I still -- that same GP I still contact about the same patient, again, he contacts me.

Q. So then if I understand correctly it can vary with the GPs depending on which primary care physicians you are dealing with?

A. It absolutely can vary with the GPs, and again, that makes things more or less difficult. In terms of getting blood levels, I have never had a problem with the GPs getting the levels of phenytoin, and of sending those to me, and so that has never been a problem that I have had, and if I ask the GPs to do it then they are very good at doing it.

Q. You seem to have been luckier than Professor Sander because he says that he has had some issues with that,

but that is something for Professor Sander?

A. Yes, you know, it is like all things in life: you remember the bad things and do not remember the good things. I mean, Professor Sander I think said that he very rarely over the last ten years prescribed phenytoin, so he may not have the experience of using phenytoin that I have had, but certainly it has not been such a big issue for me.

Q. Just to talk about the consequences if it goes wrong. If this use of phenytoin is not managed properly then small changes in the dose may lead to the acute toxicity that we were talking about earlier?

A. Yes, that is correct.

Q. And it can result in breakthrough seizures due to the dramatic decreases in the blood level of the drug?

A. Yes, so that is correct. I have to say, just on the point about legacy patients which I think are a useful group to look at because they have been on phenytoin for many years, and in fact, when you look, I mean, there was again -- there is a study and again, not to make Professor Sander blush, but it came from Professor Sander, where they looked at people who had been on long-term medication including phenytoin, and they measured the -- they sort of had a measure of the number of side effects that people had, and phenytoin,

this is long-term patients, phenytoin was about the same as carbamazepine in terms of the way that patients ranked the side effects. Interestingly enough at the time lamotrigine had worse, but that was probably because people had been started on it afresh and so the dose was being built up, so they would get side effects so they would complain, but the legacy patients seemed to be fairly stable.

Q. I would like to move now to talk about the side effects of phenytoin. I appreciate we have all mentioned a lot of other drugs, but it would be really useful just for these questions if we could focus exclusively on phenytoin and we will come on to the comparisons momentarily. A lot of these people we have already mentioned in your teach-in and in your papers, but I want to do a run-through to check we have everything.

So phenytoin can give rise to acute dose-related side effects and I think those include, one, drowsiness?

A. Sorry, yes, so it can give drowsiness, yes.

Q. Unsteadiness?

A. Unsteadiness.

Q. Slurred speech?

A. Slurred speech.

Q. Decreased coordination?

A. Absolutely.

Q. Mental confusion or cognition issues?
A. That is correct.
Q. Double vision?
A. Yes.
Q. Nausea?
A. Yes.
Q. You also mentioned yesterday that very high doses can result in a patient going into a coma; did I understand that correctly?
A. They can do, yes.
Q. Phenytoin can also cause tremors?
A. Tremors is not such a problem with phenytoin, so it can occur, it is not a problem that I find particularly difficult, and again, tends to be dose-related.
Q. You have also explained that phenytoin can trigger rare but potentially serious idiosyncratic side effects.
A. That is correct.
Q. So that would be the rashes you referred to yesterday?
A. Yes, so the rashes we see with many of the anti-seizure medications and that usually just involves taking them off. We are more concerned with the rarer allergic reactions that can occur like Stevens-Johnson Syndrome.
Q. Can you explain to the Tribunal what that is? I have Googled it, but it would be better if you explained it.
A. So allergic reactions come in degrees of severity,

a rash is one, and it is like a measles rash and so people know when they have it and then they come off the medication, but also people can get a severe allergic reaction where you can start to get blistering inside the mouth, you can get fever, you can get circulatory collapse, people can end up in intensive care units, so this is a very serious reaction, which is termed Stevens-Johnson Syndrome. It may start as a rash, which is why when rash occurs we like people to come off the drug, and why when we put people on any drug, including any of the -- lamotrigine is one of the drugs of choice, we would warn people that that is something that can occur, and should they have any of those symptoms, then they need to come off the drug and see their GP.

Q. I am just moving on to some of the chronic side effects you have mentioned in your evidence. We have discussed a lot the increased risk of osteoporosis, that is something associated with phenytoin, is it not?

A. That is, correct.

Q. You said in your evidence that osteoporosis can be managed or mitigated through taking vitamin D supplements and through the use of appropriate medications.

A. That is correct.

Q. Now, Professor Sander accepts that that can help

temporarily, but he says that it does not provide a solution in the longer term, it will usually return. Is he right on that?

A. So not completely. So the matter is more complex than that. Sorry, I know you want me not to compare, but it is very difficult not to compare here, if that is all right.

So many of the drugs, so all the enzyme inducers have been associated with it, and the mechanism, as I explained, I think, yesterday, is unclear, but one of them is that they may lower the doses -- the levels of vitamin D, so we give people vitamin D.

The second thing is that there may be other specific activities on the way that the bone remodels itself, but many of the other drugs that are not enzyme inducers may also have that, so sodium valproate does as well. Usually the process for any person who is looking after somebody with epilepsy, regardless what drugs they are on, would be, first of all, to do vitamin D levels and make sure that they are adequate, and even when people are not on enzyme inducers because we live often in a dark and miserable country, we do not get enough light and our vitamin D levels are quite low, and so I find that most people end up on vitamin D.

The second thing that we do is that if there are any

additional risk factors, and that includes age or it includes if they were smoking or were on other drugs, so anti-depressants, for example, are associated with osteoporosis as well, so if they are on anti-depressants, then we would measure the bone density and at that point you can start to see whether the bone density is going down and then there are drugs which are called biphosphonates that you can actually give to prevent osteoporosis completely, so we would then put people on to those. Then that mitigates that and prevents that from occurring.

Q. So you do not accept that there are any circumstances in which you cannot deal with it, basically?

A. No, we can deal with it. The circumstances in which we do not deal with it are where we do not see the patients and they are not properly monitored, and they develop osteoporosis in any case. Osteoporosis, of course, is a large concern in the population in any case.

Q. I was just going to say the weather is proving your point of us all needing vitamin D today.

Another chronic side effect of phenytoin is facial distortion through the coarsening of the facial features, you said that has the greatest association with phenytoin sodium, is that correct?

A. It does, yes, and again I think -- so the concerns from

that really came out of a study done in the 1980s, and they found about 30% of an institutionalised population, many of whom had learning difficulties, would have coarsening features on phenytoin. When I look at my legacy patients, it is not something that is such a big issue. There may be -- I am trying to think -- there are certainly not patients complaining about it. I can certainly think of one or two patients in whom it is something that I have seen. It is something whereby, if I was to start somebody who was very young on phenytoin, I would explain to them that that is a specific risk, but it is rarely a problem in my practice.

Q. Phenytoin is also associated with gum-related side effects. I understand those side effects to be gum swelling, tenderness and bleeding due to gingival overgrowth?

A. Yes, which is just the gums overgrowth, that is right.

Q. Can you explain what that overgrowth is and what it means?

A. Yes, so it is just that the gums start to overgrow the teeth and that can have a cosmetic effect. It can also have an effect because it means that it may be more difficult for people to manage things like plaque and so forth, and so an increased risk of gum disease.

Again, that is a side effect of phenytoin. I mean,

phenytoin has been around for 80 years, and dental health was a lot worse 80 years ago than it is today, and it was seen a lot. In fact, since people have used -- have improved dental health, and again, this is something I warn people who are going on to phenytoin, that they should get regular check-ups with the dentist when they are on phenytoin, they should maintain good oral hygiene, the risk is actually quite a lot smaller, so probably of the order of about 10%, whilst if you looked 50 years ago it may have been more like 30% or 40%, so it has dropped quite considerably.

It is a problem? It can on occasions be a problem, and I can think again of a patient where we ended up deciding to take the person off phenytoin because of that problem, but for the majority, the vast majority of people that I have on phenytoin, most people who start it anew and legacy patients, it is not such an issue.

Q. But it can cause it basically to cover the teeth, so in some situations you would take a patient off --

A. Yes, and it is reversible so it then improves and gets better, so other drugs, I know again -- sorry, I do apologise, you did not want me to compare -- valproate also has a similar sort of side effect, not as severe as phenytoin, I am not sure how common it is, but valproate again, if it occurs you take people off and it improves.

Q. Professor Sander says that these gum-related issues affect well over two-thirds of people taking phenytoin for more than a few months; does that accord with your experience?

A. Absolutely not, actually, and I do not think it accords with my experience or indeed the literature. So it depends on what population you are looking at. Again, people may -- many of the studies, again, from the 1980s, were done on institutionalised patients who did not have particularly good dental health. When you look in a GP's practice, which was done, the instance was about 10%, which would be about my experience, about one in ten people experience it, and then of those one in ten people that experience it, not all of them see it as a specific problem, it is something that they will have, but they may well decide to remain on phenytoin because they have good seizure control. So I certainly again -- and I apologise that this is anecdotal, but I can certainly think of a patient of mine who has been on phenytoin for a very long time who has had gum problems with it, but people have tried to in the past take her off phenytoin with a disastrous effect on her epilepsy, and so she has remained on phenytoin despite the gum problems.

Q. This is what we were talking about at the start, that

some patients will decide to tolerate it, because they want to achieve seizure-freedom?

A. Yes, and that is true of a large number of the drugs that we use, and I would very much like to have drugs which have no side effects and which are very efficacious, and I would very much like to use -- not to have to use drugs that have side effects, but at the moment we do have to use these drugs because in many patients they are the only way in which we can get seizure-freedom.

Q. Now, I just want to discuss some of phenytoin's interactions with drugs other than ASMs. I think we mostly agree on this but I want to run through and make sure that I am correct in saying that. If a patient has cancer then phenytoin can interact with some forms of chemotherapy, is that right?

A. Yes, it can. I mean, I am happy to go through that. I think there is 400 drugs that are listed as drugs in which phenytoin can interact, similar to carbamazepine and phenobarbital.

Q. That is part of the reason why Professor Sander says phenytoin can be associated with low cancer survival rates; would you agree with that?

A. One of the reasons why phenytoin would be preferred in people who have cancer and are on chemotherapy is

because absolutely you would reduce the efficacy of the chemotherapy. That can be addressed sometimes by increasing the doses of chemotherapy which was what was done when phenytoin was used more frequently in the past.

Q. It has to be managed, then, in part?

A. Yes, so when people with brain tumours, which is a cause of epilepsy, need to go on to anti-seizure medication, again, as Professor Sander said, we would use lamotrigine or levetiracetam as the first-line therapies, and only when, you know, therapies have failed will we then be moving on to third-line therapies in those cases.

Q. I think you also agree that phenytoin can cause an increased risk of cardiovascular disease; is that correct?

A. I think my answer to that question is nuanced, actually, because it has been a debate for a long while, and as Professor Sander said, there is no doubt that there is evidence that it can increase cholesterol. That is something again that we unfortunately all put up with, and it can be managed with statins.

Back in 2012, the evidence was, you know, anecdotal, it can put up cholesterol, and that could be managed by reducing cholesterol, and it is only recently, so it is

only -- I think it was 2021 when a paper came out which was a large epidemiological study that seemed to indicate that enzyme-inducing anti-seizure medications had an increased risk of cardiovascular disease, and cerebrovascular disease. The majority of those patients were probably on carbamazepine rather than phenytoin, and then interestingly enough, in the same year, in fact, just predating that, there was a study which showed that there is no difference between enzyme inducers and non-enzyme inducers, so completely opposite, and you may ask what is the difference between these studies, and it is something that I think is taxing us at the moment, and something that needs to be looked into, but it is not absolutely clear.

The study that did show a difference said that they looked over a longer time period, but then there is a problem with that study. So that study began recruiting in 1990 so it looked at anti-seizure medication use from 1990. The drugs like levetiracetam was not licensed until 2000. Lamotrigine, which is now the most used drug, was not licensed until 1992.

So if you look at what has happened, what I think may have happened in that paper, is that the people who were on enzyme-inducing drugs were the people who were started who were on that in the beginning of that

period, and then later on the non-enzyme-inducing drugs were introduced, so when you start to look at survival and cerebrovascular disease you are looking at people from a later date, or who probably presumably developed epilepsy at a later date.

Now, why that is important is that there has been a 70% drop in cardiovascular disease over the last 50 years. Over the last 30 years there has been at least a 17% to 20% drop in cardiovascular disease. So it may well be that that paper was biased because the people who were on the enzyme inducers were being given it earlier and the other ones were being given it later, so it may be a temporal thing. So it is a complex thing, but it just -- and I hope I explained that well enough, but it just means that there is still -- that controversy remains and it is a controversy that is yet to be resolved.

So I completely agree that enzyme-inducing drugs will increase cholesterol levels, I completely agree that people with epilepsy have an increased risk of cardiovascular and cerebrovascular disease whatever drugs they are on and the reasons behind that are not absolutely clear, and I completely agree that people need to have their other cardiovascular risk factors including smoking, high blood pressure and cholesterol

managed, and perhaps managed more closely than the rest of us.

Q. Just some further side effects that Professor Sander mentions that I just want to check with you. Professor Sander says that an enzyme-inducing ASM -- as an enzyme-inducing ASM, phenytoin can impact the normal working of the liver because of metabolic dysfunction?

A. Sorry, again, this is a -- it is a sort of nuanced question again. So it alters the normal working of the liver in that it increases the activity of the enzymes that are there, yes, but the liver will still be working, it does not -- it is not liver dysfunction, it is in fact, if anything, liver over-function.

Q. As an enzyme-inducing ASM, phenytoin can also lead to -- and I think you have also referred to this -- the lipid abnormalities, so the increase in cholesterol?

A. Absolutely, and that is well recognised.

Q. Thyroid abnormalities?

A. So this is not -- so, again, this is again, a sort of nuanced question because phenytoin can reduce the levels of some of the thyroid hormones. The way that the body reacts is that we have a feedback loop, so that the thyroid will then produce more of the thyroid, so this is not something that is ever clinically or rarely ever clinically a problem.

Q. Sex hormone abnormalities or leading to sexual dysfunction?
A. Yes, so it can reduce some of the sex hormones, and along with many of the other anti-seizure medications, it can reduce sexual desire.
Q. Metabolic dysfunction of blood vessels?
A. I am sorry, I am not quite sure if I understand that correctly. There is no specific or very little evidence that it actually has a direct effect on blood vessels. That was purely a -- one of the theories that was put forward for enzyme-inducing drugs having an effect on cerebrovascular and cardiovascular disease.
Q. Phenytoin is also associated with -- I do not know how to say this one -- hirsuitism, excess hair?
A. Hirsuitism, yes, so again, this is something it shares with other drugs, and it is not -- I mean, again, it is something that it shares with valproate, in fact valproate is probably worse than phenytoin in that respect.
Q. But it is something that phenytoin has?
A. It is something that phenytoin has, yes.
Q. And it can trigger severe acne?
A. It can trigger acne.
Q. A further acute potential side effect of phenytoin is blurred vision?

A. So the blurred vision, that is not really -- that is more an acute side effect, and that is usually because the dose is too high and something that we can adjust.
Q. Sorry, I spoke too quickly, I did say a further potential acute side effect, so we are agreed on that?
A. Okay, so that is similar to the other acute side effects that I mentioned previously.
Q. Another potential acute side effect is involuntary movement of the eyes?
A. Yes, so that is -- again, that is something that is seen with the acute side effects and that is an effect on the cerebellum which we see with many of this drug class.
Q. A further chronic side effect of phenytoin is pernicious anaemia?
A. So again, this was a problem that was seen in the past, and is not so much a problem now, which is that phenytoin, along with the other enzyme inducers, will decrease the vitamins folate and B12, and that is because they increase the breakdown of those vitamins. This has not been such a problem more recently because people have adequate diets. When people are on restricted diets, like, especially vegans, they can also develop that, irrespective of whether they are on phenytoin, but if they were to start phenytoin I would make sure that I monitored the blood levels of that

vitamin.

Q. You heard Professor Sander discussing this co-morbidities issue this morning about cardiovascular risks and endocrinological and cerebrovascular changes, so strokes, heart conditions, things like that. That is his specialist area, is it not, these co-morbidities of --

A. Yes, his specialist area is epidemiology and looking at the longer term outcomes.

Q. If we go to paragraph 28 of Professor Sander's position paper which is at {XE6/9/7}. Professor Walker, you should have that in written form in front of you.

A. Yes.

Q. Could you just go to the previous page, page {XE6/9/6}, the quote starts there. If we could just read the whole of paragraph 28, so we can turn the page once the panel confirm.

A. Yes.

"Professor suggests that he is unaware 'of any evidence' that patients taking a strong enzyme inducer, such as phenytoin ..."

Q. Professor Walker, you do not have to read it out, unless you want to. It is quite a very long paragraph.

A. Yes, I am too easily led, I'm afraid. Yes.

THE PRESIDENT: Would you turn the page?

MS MORRISON: Would you turn the page? {XE6/9/7}.
THE PRESIDENT: Could you put the whole page on? Thank you.
(Pause)
MS MORRISON: Professor Sander outlines there the work he has done and why he reaches the view he has about the association with use of phenytoin with lower life expectancy. I am sure you do not fully agree with it, but do you accept that Professor Sander's view is a reasonable one in the light of the evidence he cites?
A. No, I do not. So again, I think we have to look at this in context. So he states that people on phenytoin have a lower life expectancy. There is, as far as I know, no evidence to indicate that. He states that work from his group showed that cohort enrolled in the study in the 1980s, that there was co-morbid conditions, most of that was due to vascular disease and I am very much aware of that work, and it was very important work, indicating that people with epilepsy have an increased risk of vascular disease.

The recent study suggested a decrease in mortality rates amongst people with epilepsy, but that is -- has to be taken in context, and as I say, one of the problems in looking over time is that the mortality rates from cardiovascular and cerebrovascular disease have dropped overall in the population.

So the only way of really demonstrating this convincingly would be to look at what has happened to the general population and then compare against people given enzyme-inducing and non-enzyme-inducing drugs and the only large study that has done that was the study, 2021, published in Epilepsia, with, I think, Owen Pickrell is the last author, and there, interestingly enough, they showed, as Professor Sander had showed, all the way back in the 1980s that cerebrovascular and cardiovascular disease are more prevalent with people are epilepsy, but they showed no difference between enzyme inducers and non-enzyme inducers.

So I think that hard distinction that Professor Sander makes is to my mind overstating the case. Whether there is a benefit in non-enzyme inducers on those particular things I think is something that still needs to be resolved. It certainly was not resolved in 2012, and I certainly do not know of any evidence to indicate that people on phenytoin have a lower life expectancy.

Q. Even though you and Professor Sander disagree over that, I think happily though your view is still that phenytoin is and should be a third-line treatment as categorised by NICE?

A. Absolutely so, as I -- absolutely, and I think there is no disagreement between Professor Sander and myself on that point.

Q. And as a third-line treatment it is rightly used for people who are resistant to other medications, you have mentioned a number of other medications you would try first?

A. Yes, absolutely, and the medications that I would try depends upon the person that I have in front of me, and the impact that those side effects may have, and so, yes, I will try other medications first-line when I am adding it into people who have refractory epilepsy.

There is a time when we do use it first-line in people without previously having had medications, and that is when people have very prolonged seizures, and then we will load up with phenytoin because it is very effective. In fact, it is the most -- so far it has been shown to be the most effective at stopping those seizures.

Q. So just on that latter point, that is an emergency situation in the hospital; I understand that that is an intravenous application of phenytoin rather than capsules?

A. Yes, so you are absolutely right, so we give -- so when people have prolonged seizures, if they have prolonged

convulsions then obviously you do not give things orally, you can just inject things, we would inject phenytoin and then we would maintain people on phenytoin afterwards, and how long we maintain them and whether we change depends upon individual circumstances, and then there are people, for example, who come into hospital who have prolonged seizures, so there are different seizure types and we have people who come in with prolonged seizures where they have presented just with confusion, and there are risks attached to giving intravenous medications, and so sometimes I do load up, and I have loaded up, in the last five-years, with phenytoin capsules, so I have given somebody 1,000mg of phenytoin orally to get good control of their continued seizures, rather than giving them intravenous phenytoin.

Q. But in general terms, phenytoin is a drug which is prescribed when almost all other anti-seizure medications, a combination of ASMs have failed, so you have gone through first --

A. Yes, no, absolutely, and I think both Professor Sander and I are clear that there are drugs that we would use ahead of phenytoin in the treatment of people with epilepsy.

Q. That leads very nicely to my next topic which is what newer anti-seizure medications bring. I think you

basically just said it, but I understand you to accept the overall profile of the side effects of some new ASMs may be less significant than those of phenytoin?

A. Absolutely, so that is true of lamotrigine and true of levetiracetam. Some of the other drugs, the side effects may be comparable, and again, we have been using a lot of cenobamate which is a new anti-seizure medication, newly-licensed, it seems to be very effective, which is the reason we use it, it has large numbers of side effects, very similar to the side effects of phenytoin, we do not know what its chronic side effects are yet, but we are using it to try and get seizure control in people who have tried almost all other drugs.

Q. Some of those newer drugs will have better a safety and tolerability profile?

A. That is true, particularly lamotrigine and levetiracetam.

Q. I understand just on some figures, about 50% of people respond well to the first medication tried?

A. Yes, that is correct.

Q. And almost all ASMs are equally effective in that regard?

A. That is true.

Q. I just wanted to confirm something you said yesterday,

I just wanted to make sure I have understood it properly. You said from your teach-in yesterday that only 5% of people become seizure-free once you get to using third-line treatments, is that right?

A. That is correct, yes.

Q. Is that 5% of the total population, or is that 5% of people that are tried on third-line drugs?

A. I am sorry, that is 5% of people who are tried on any drugs.

Q. Tried on any drugs, it is the entire patient population?

A. So if you take the patient population and then try somebody on a drug, then you find about 5%. So the number of people who become seizure-free is very much predicted by the number of drugs that people have tried, so overall for the first drug it will be about 50%, second 25%, and then it drops. You get to the sixth or seventh drug you are looking at somewhere between 5% and 10%. If you get up to the ninth or tenth drug, then you are looking at very few people, and that is not predicted by the drugs that you are necessarily trying, so that is epidemiological evidence that those drugs are having those effects.

Q. So essentially phenytoin, like the other drugs, will sometimes work at that stage, but sometimes not?

A. Absolutely.

Q. I just wanted to very quickly cover why phenytoin is a third-line drug, and we have already talked about the issues with phenytoin, so I think we can do this fairly rapidly, but let us see. You have said that phenytoin is a third-line treatment mainly or primarily because of its complex pharmacokinetics?

A. I do, yes.

Q. It is also due, though, to some of its potential long-term side effects?

A. No, not particularly. So it is very interesting again to hear Professor Sander's evidence that he would not use enzyme-inducing drugs at all, and certainly he has his particular reasons for that.

Back in 2012, carbamazepine, which is as strong an enzyme-inducing drug as you can was first-line; back even in the most recent guidance it is second-line treatment. So you have to wonder what is the difference between phenytoin and carbamazepine, and the main reason that phenytoin has fallen below carbamazepine in its use is because of its pharmacokinetics, because it is difficult to use.

Q. Could we just go to paragraph 2.5 of your fifth report, please, which will be at {XE4/5/2}. So it should be in tab 5 of the bundle that you have.

A. Yes, I have that, thank you.

Q. I just wanted to clarify something, because in this paragraph you say:

"As I set out in my first report, in my opinion, phenytoin's place as a third-line treatment is primarily due to its complex pharmacokinetics and some of its potential longer term side effects ..."

So can you just clarify what you were referring to there as potential long-term side effects as being relevant to the third-line status?

A. So again, so if you were going to choose a non-enzyme against an enzyme-inducing drug, or say, longer term side effects with osteoporosis, you may choose something that is less likely to cause osteoporosis than phenytoin if there is equipoise in choosing those two drugs.

Q. Phenytoin is third-line, so it is also partly due to its interactions with other drugs?

A. That is correct, and that is due to its pharmacokinetics and its interactions and liver enzyme-inducing.

Q. And the need to manage its narrow therapeutic index, which I think leads off of that?

A. Yes.

Q. I understand that your position is, though, that phenytoin is not a third-line treatment due to a lack of efficacy?

A. Absolutely not. So it is a third-line treatment because

it can be efficacious, and I think, again, if it had no efficacy as third-line treatment, then it would not be something that we would use ever or at all. The fact that we would all consider it and we all do use it on occasion indicates that it is because we think it can work when other drugs have failed. So very much so, that it is efficacious.

Q. There has been a bit of a back and forth between you and Mr Hawkins about the relevance of efficacy to NICE's analysis in 2012, but I think the simple point, and let me just check if this is right, because if it is right, we do not need to trouble too much with it, is that when NICE were discussing efficacy in the guidelines, they are talking about a combination of efficacy and tolerability, is that right?

A. Yes, so I think there is a confusion that occurs is that, you know, efficacy would to most of us be how well something works. There seems to be sometimes in some of these reports an interchange between efficacy and retention, so whether somebody stays on the drug, and whether somebody stays on a drug is not just efficacy but also tolerability.

Q. That is of course the right metric for NICE to look at because there is no point in having a super effective drug if no one will stay on it, so that is why they are

looking at both together?

A. Absolutely, but if -- again, it is nuance, it varies from person to person, so these are population considerations, and, yes, so if somebody does not tolerate, or if a drug is completely intolerable, or it has side effects that means that you would never give it to somebody, then it is a drug that is withdrawn, so we had that with retigabine, which turns people blue, literally, and gives them -- the retina, the back of their eye turns blue as well, and this was not discovered for a while, so it was launched and marketed and we were using it, and suddenly this side effect started to occur and then of course the drug was withdrawn, MHRA withdrew the drug.

It first of all gave us warning and then said withdraw and vigabatrin similarly, vigabatrin was a fantastic drug when we first started using it, in fact when I was using it with Professor Sander, and we had many people coming seizure-free, but then -- and in fact I still have some people on vigabatrin, but there is a risk, a substantial risk, of visual loss on it, and so I have people on vigabatrin because they are rendered seizure-free by it and nothing else has worked, and I monitor -- I get their vision monitored every six months to make sure that they are not getting the

visual loss that has been associated with it.

Q. So it is that measure of efficacy combined with tolerability was one of the reasons why phenytoin was marked as a third-line drug in 2012?

A. Yes, so the reason why, again -- again, I apologise for repeating myself -- so it is not the efficacy that moved it down to third line. The reason why it became third line was because it has this difficulty in using which means that you can get these acute side effects, and those -- that really was, to my mind, the main reason why it moved down. I am sure Professor Sander would like carbamazepine to be moved down to third line as well, and perhaps in his practice it is third line, but -- and that is because again of the enzyme induction, but overall it was moved down by NICE, the main reasons why it was moved down there, and generally the NICE guidance is -- has two contributors, so it has an economic contribution, and they make an economic contribution which would be the assessment of the value of the drugs and I think I am not an expert in that area. It also has a contribution from a panel of experts who will then say: well, hold on, you said that does not work but in fact in our experience it does, and we would like that included, and then it also goes out to the general -- did I say, general population -- to

the general epilepsy community, where we can then comment on it, and so, for example, in 2012, I was part of a group that was commenting on the guidelines as they were sent out, and so where drugs are in that list is a combination of different things, but often it is because that has been determined by practice, and certainly phenytoin had moved down to third-line and predominantly because it was difficult to use.

Q. So that status as third-line is really the reflection of consensus view, so whilst you and the Professor may differ on some issues, it is very much the consensus view that phenytoin is third-line?

A. I think it is consensus view and I think it is the consensus view of Professor Sander and myself. I am aware -- you know, you have the other third-line drugs, which ones you are using first differs, but also there may be second-line drugs that you will not want to use and again, the easy drug to use is -- to take an example is topiramate, so topiramate can cause language difficulties, it can cause renal stones, so if there is a strong family history of renal stones or you have had renal stones you would not be using topiramate and I would use phenytoin ahead of topiramate, so it is about the person you have in front of you.

Q. I think we discussed this earlier but we talked about

the fact that there are at least some anti-seizure medications that you accept have a lower side effect profile than phenytoin, and you mentioned lamotrigine and levetiracetam -- gosh, I am never going to get this right -- levetiracetam.

A. Levetiracetam, yes.

Q. Is Professor Sander right to say that lamotrigine does not have any chronic side effects?

A. Again, so this question is more complex than just that. So if you say: does it have any side effects with long-term use, and the answer is mostly it does not, and that is why we favour lamotrigine. It does cause acne and I have seen acne being a problem with long-term use of phenytoin, such that I have one person who has had to come off it. I have had another, recently actually, skin condition psoriasis, which was exacerbated to such an extent by lamotrigine that again, even though the person had achieved seizure-freedom, we are moving them on to another drug. So in the longer term it does have some side effects, but it does not have those other concerning side effects, the evidence indicates it does not cause osteoporosis, for example, it does not alter lipid metabolism.

Q. So those sort of considerations would apply to levetiracetam and lacosamide?

A. So levetiracetam, similarly, we do not know of any long-term side effects; levetiracetam has been licensed since 2000, but it has been used extensively. I do not know of any long-term side effects. It has side effects that may mean that again it can be difficult, and it has side effects long term which means it can be difficult, so it can be associated with severe depression, it can be associated with psychosis and again -- and aggression, so I have had to take people off levetiracetam because of those. We may try to keep them on it for a while and then eventually they just cannot tolerate it and end up coming off it, so it has side effects that are concerning, but it does not have -- again, there is no evidence to indicate that it has the osteoporosis and the alteration of lipid metabolism.

As Professor Sander said, it is a drug that is mainly excreted by the kidneys.

Q. Lamotrigine and levetiracetam, neither of them have enzyme-inducing properties is essentially --

A. No, they do not.

Q. No. And they have less propensity for drug interactions, I think?

A. They have much less interactions.

Q. I think one of the points that you make in your expert reports is: look, you know, with newer drugs we might

not know the whole profile of side effects, and so in a sense, phenytoin is better the devil you know, but do you accept that at least for these drugs that we have just been discussing that we do know most of their side effects by this point?

A. So again, for lamotrigine we have a very good idea of the side effects, levetiracetam we have some idea, it has been around for 20 years, so we have got 20 years of use. Some of the newer agents have been around for very short amounts of time and I think, you know, the lesson learnt is exactly the lesson that Professor Sander said in his career and my career as well, we have had four anti-seizure medications that have had to be withdrawn, we had one anti-seizure medication, felbamate, that had a rare side effect that resulted in the death of people, so resulted in liver failure and failure of the bone marrow. Felbamate was marketed in the US a bit like in Time magazine people used to come to my clinic and say: why am I not on this drug, it cures epilepsy, it was a good drug, but it was only when they started to see widespread use that they started to see people dying from it and had to withdraw it from the market. Retigabine was another drug, we had been using that for a while, before this blue discolouration was noted, and then there was initially a warning and then eventually

the drug got withdrawn.

So, you know, we have to be very prudent when we are starting these new anti-seizure medications, and even medications that have been around for a while, so vigabatrin was around for a number of years, I think seven years, seven or eight years, before it was noted to have the problems on visual fields, and those are quite profound problems, you know, a third of people would have quite significant loss of their vision to the sides, and it was not until we started to see that with the widespread use.

So I would say that with all new anti-seizure medications we have to be particularly careful about what we see in the longer term, and with phenytoin we have 80 years of experience, we have, you know, this is the drug that most people have been on for the longest. The only older drug that we use is phenobarbital, and phenobarbital does have -- and there is evidence that indicates that it has more side effects, but again, those are the two drugs that we have the most and the longest use and experience of, and neither of them have been recommended for withdrawal by MHRA in contrast to others.

Q. But Professor Sander is right to say that since the 1980s the testing of drugs has been far more extensive?

A. So pharmacovigilance increased dramatically in the 1980s because of thalidomide, absolutely, so there has been greater pharmacovigilance, greater pharmacovigilance of all drugs, including phenytoin, so you are correct that side effects, that may not have been noted in the past, may be picked up more quickly, but it can still take a while before these side effects occur.

Phenytoin -- sorry, vigabatrin is an example: you can only pick up side effects that you look for, so vigabatrin, we never imagined that it would affect the visual fields, why should an anti-seizure medication affect vision? It was not until people started complaining and people started to get testing that we started to realise the extent of this problem. So that went on for seven years before we actually picked that up and before it was -- in fact, it is still used because it is effective, but with extreme caution.

Q. But Professor Walker, I think I know the answer to this question, but I was your patient who walked into your clinic tomorrow and I said: look, I would rather take phenytoin rather than lamotrigine because we know more about phenytoin's side effects, what advice would you give to me as my doctor in those circumstances?

A. I would say that the evidence that we have indicates that lamotrigine is likely to be better tolerated, there

is no evidence that lamotrigine is more efficacious than phenytoin, in fact, the evidence would seem to indicate that phenytoin may be more efficacious, and that I would recommend that they use lamotrigine first-line, and that if lamotrigine fails and they were aware of the side effects of phenytoin and those are the side effects that they were happy to risk or take, then I would try phenytoin next, on the basis that phenytoin can work when lamotrigine has failed.

Q. Would you use it next after lamotrigine, seeing as it is first-line to third-line, would you not use it first-line or second-line first?

A. It depends on the person and the discussions that we had. I mean, there are other drugs that I would recommend ahead. I would usually use lamotrigine and then levetiracetam. But I mean, I can give an example, I have a patient at the moment in fact, somebody I saw on Monday, where, you know, their greatest concern is -- they have psychiatric problems and their greatest problem is the psychiatric side effects of anti-seizure medications. In that case, I will not be using levetiracetam, and I know that levetiracetam can cause those psychiatric problems. So although it is recommended as first-line, it is not something that I would use first-line in that person, and if you were

to say to me: where down the line would I use it, there is every chance I may be using phenytoin ahead of it because it would not have those particular problems.

Q. Just drawing everything to a close, it is pretty clear that you and Professor Sander have different views on phenytoin within the third-line bracket, I think that is obvious to everyone, but the President asked you a critical question yesterday about whether or not due to clinical judgments different clinicians might have a different batting order when it comes to selecting third-line drugs. You agreed with that, did you not?

A. I do, and I think that was a very important point, that with the first-line, the first drugs that we use, we have considerable evidence about what we should be using, and I think there is no doubt that, you know, lamotrigine, levetiracetam are there. When it gets beyond that, it really is down to clinical judgment, and people will have different batting orders, but the important thing is that, you know, we always have somebody in front of us, and the drugs that we will use depends upon how quickly we want to get seizure control, it will depend upon what other drugs the person has tried, it will depend upon what side effects that person is willing to accept or not accept, it will depend upon our knowledge of sometimes the longer term side effects

of these drugs, and how easy the drugs are to use.

So there is a whole host of things that we will use, and it is not prescriptive, and so it will change, and it will alter, and some people will prefer one drug above another, and very often the drugs that you prefer are the drugs that you feel more comfortable with, or the ones you have used more frequently. So it does vary from person to person.

Q. But would you, in principle, look at the first-line and the second-line drugs first, you mentioned just two of the first-line drugs in your answer there, but you would look first at the first and second-line drugs?

A. I would generally use first and then second-line, and I think my approach would be very similar to others, and, as I say, I have seen -- one of the other things that is difficult within our practice is that these are not things that are readily available for us all to know and discuss. So every one of us is a bit in a silo, we do discuss outside and we go to meetings and discuss what we would use and how we would use them. I do see how other people and other neurologists, and other neurologists with expertise in epilepsy use drugs because they refer in to me and I have seen the drugs that they use, and I have seen that they are using phenytoin, so I do not think my practice is unusual.

Q. But everyone has agreed, as we have just discussed earlier, the consensus is that phenytoin is a third-line drug?

A. I think there is no doubt that phenytoin is a third-line drug.

MS MORRISON: That is all my questions, sir, unless the Panel has any questions.

THE PRESIDENT: Thank you very much. Professor, we are going to rise for lunch. When you are come back, I am going to, at risk of trying your patience, retread a number of points.

A. Yes, that is fine.

THE PRESIDENT: The reason I am doing so is not to elicit further evidence from you but to ensure that I have my understanding of the evidence you have given right. So I am going to go through a few points. It will take some time, but I hope you will feel entirely free to correct the nuances and get me on the right track. So that is the agenda next.

I do not know how we are doing for time. If we say that is going to take about half an hour, ought we to abrogate the lunch break a little bit because I am very keen that we have exactly the same time with Professor Sander as we have had, Professor, with you?

MR JOHNSTON: Sir, it may depend a little bit when we are

1 going to finish this evening.
2 THE PRESIDENT: I have a meeting out of this court at 4.30,
3 so I am quite prepared to sprint, but I think it
4 means --
5 MR JOHNSTON: I will not ask you to sprint, sir. Shall we
6 assume 4.15 is a hard stop or would it need to be
7 earlier?
8 THE PRESIDENT: No, it need be no earlier than 4.15, and we
9 could probably run to 4.20.
10 MR JOHNSTON: As always with cross-examination, sir, it is
11 going to depend slightly on the length of the answers to
12 the questions.
13 THE PRESIDENT: Yes, it is.
14 MR JOHNSTON: Can I suggest that we come back at 1.45, if
15 that is acceptable to the Tribunal?
16 THE PRESIDENT: Professor, you have been incredibly helpful.
17 If we were to say we will resume at 1.35, would that
18 cause you in difficulties?
19 THE WITNESS: No, not at all.
20 THE PRESIDENT: In that case, if that is convenient to
21 everyone else --
22 MS MORRISON: That is fine.
23 THE TRANSCRIBER: Could we have 45 minutes, please?
24 THE PRESIDENT: I understand.
25 MR JOHNSTON: Sir, the other possibility, if I am left with

a handful of questions or the Tribunal has questions, I know it is perhaps slightly less convenient for Professor Sander, we should check with him, but we could finish tomorrow morning and also start earlier.

THE PRESIDENT: I understand. Well, let us see how we go. We will run for three-quarters of an hour and resume at 1.45.

Professor, you will recall my warning yesterday: do not speak about your evidence to anyone. I am sure you will not want to, but I will see you back here at 1.45. Thank you very much.

(1.01 pm)

(The short adjournment)

(1.47 pm)

Questions by THE TRIBUNAL

THE PRESIDENT: Good afternoon, Professor. Before we begin, just to say that in fact I was misinformed about my diary, I do not have a meeting at 4.30, no 4.15 sprint is required, so we should have time to finish today.

MR JOHNSTON: I am very grateful. Just to add to the picture, Professor Sander, I understand, has cancelled clinics, as has Professor Walker, to be here, so he would not be in a position to come back tomorrow morning. If we do not have a hard stop at 4.15 that gives us a bit of flexibility.

THE PRESIDENT: We have flexibility. It is good all round, thank you.

Professor, could we bring up {XG/307/1} on to the screen? It is a document you are very familiar with, but you should see it.

This is the guidance regarding changing products with regard to anti-epileptics, and I just want to start by explaining what I am going to be asking you about and what I am not going to be asking you about.

I am going to be asking you about the change of a patient into a new regime, in other words, let us say, someone who is on phenytoin and being moved away from that to a non-phenytoin drug, so that is what I mean by a new regime or regime change.

What I am not going to ask you about is change within the established regime, in other words, where one is continuing a phenytoin treatment but moving from, let us say, a branded phenytoin product to a non-branded generic. So just -- you understand the difference I am talking about?

A. Yes, I do, thank you, sir.

THE PRESIDENT: Just to be clear, this document is dealing with the latter case, where one is continuing a phenytoin treatment but one is saying if one is doing that, you should be very careful when you shift from one

manufactured product to another.

A. Yes, sir.

THE PRESIDENT: Thank you.

So let us start with a new patient who is diagnosed epileptic but who has not been treated, and there will be a number of drugs that you will try before you come to phenytoin in the case of that patient.

A. Yes, sir, yes.

THE PRESIDENT: Would it be fair to say that that is because of improvements in medical understanding, more drugs coming on to the market, more choice for the physician?

A. That is correct, sir.

THE PRESIDENT: So that would explain the decline of use of phenytoin because simply over the years we have discovered better drugs?

A. We have discovered drugs that have -- may have -- some of them have better side effect profile, some of them are easier to use, especially in combination.

THE PRESIDENT: I am very grateful. I mean, there will be a number of clinical reasons why one will choose one drug over another?

A. Yes.

THE PRESIDENT: I am certainly not suggesting, and you are certainly not accepting that there is a fixed running order as to how to do it as you, and indeed

Professor Sander have said, the patient before you matters most, and you need to consider what is most appropriate for that patient.

A. Yes, sir.

THE PRESIDENT: It may be that what is considered most appropriate for that patient will differ from physician to physician?

A. Yes, sir.

THE PRESIDENT: This is not a -- this is a judgmental exercise, and the skill and years of experience you accumulate will lead to different calls in the hard case?

A. It will, sir, yes, and different opinions.

THE PRESIDENT: The general agreement is that phenytoin is a third-line drug, so you are actually only going to get to it after you have tried other drugs in order to see whether that deals with the seizures?

A. Yes, sir.

THE PRESIDENT: So pretty much by definition at least these days, and during the relevant period, before you get to phenytoin, the patient will already have been tried on certain drugs?

A. They will, and they will already be on certain drugs.

THE PRESIDENT: And they will already be on certain drugs, that was my next question, so it will be a question of

inserting phenytoin into an existing drug regimen?

A. Yes.

THE PRESIDENT: Which has not quite worked?

A. Yes, sir.

THE PRESIDENT: Thank you. So we are agreed, then, that the demand in terms of new patients for phenytoin is going down?

A. Yes, sir.

THE PRESIDENT: So the demand that is persistent is a latent demand: it is those patients who were prescribed phenytoin in the past and they are, for reasons that I am going to explore with you, sticky?

A. Yes. So it will fall into two groups: those -- the majority, as we have heard, of patients will be those who are already on phenytoin and then there will be some in whom we will try phenytoin because other drugs have not worked, and then if it is successful, then they will remain on phenytoin.

THE PRESIDENT: Indeed. Now, those I would class as the new patients.

A. They will, yes.

THE PRESIDENT: In other words, these are the ones which are represented by a decline in demand. I am certainly not saying that that demand will vanish. What I am suggesting, and I think you are agreeing, is that as

regards people who are not on phenytoin ever, they are diminishingly likely to go on phenytoin now because of the alternatives?

A. Yes.

THE PRESIDENT: I am certainly not saying, and you are not saying that it never happens, it is just happening to a diminishing degree?

A. Yes.

THE PRESIDENT: Moving then to the patients who are not new, those who are on phenytoin, they are, I am going to say, sticky in their demand, in other words, they are not going to shift very easily away from phenytoin, and what I want to do is explore with you, if I may, the reasons why that might be.

A. Yes, certainly, sir.

THE PRESIDENT: Let us take a patient who has been established on a phenytoin regime, obviously other drugs will be involved as we have discussed, who is experiencing a problem in the form of either increasing side effects or a seizure. In those circumstances, what would typically happen?

A. So, I mean, there are two separate questions there. If they are just side effects then we would adjust the medication to try to remove those side effects, and that usually just involves reductions. In some cases, we

will end up reducing somebody's medication, whether it be phenytoin or another medication, because of the side effects, and then they may have a recurrence of seizures, and then that often becomes a difficult question about whether the side effects are acceptable and how do we manage that, and then the -- so that's those patients.

The other patients in whom the combination they are on is not working, then what we will generally do is try and reduce the number of medications that they are on and then add in a further medication, and one of the things that we will all avoid doing, both myself and Professor Sander, I know, we avoid trying to get people on multiple, you know, five, six medications, and we will tend to have a maximum of about three, so if they are on three we will try and remove the one that we think is working least well and replace it with another.

THE PRESIDENT: Again, correct me if I am wrong, but you are drawing a clear distinction between the patient who is not seizure-free having been seizure-free --

A. Yes.

THE PRESIDENT: -- and the patient who is continuing to be seizure-free but is suffering from a change in the side effects from their medical regime?

A. Absolutely, sir.

THE PRESIDENT: Starting with the first case, the patient who, let us hypothesise, for a material period of time has been seizure-free, suddenly gets a seizure. How common is that? Is that something which is quite rare?

A. No, and in fact there are reasonably good studies of that. So if you look at people who are seizure-free, have been seizure-free for two years, and then you look for the next two years, then you may find that somewhere between 10% and 20% of people may have a recurrence of their seizure even though they have been seizure-free for two years.

THE PRESIDENT: Right. Now that of course is very serious.

A. That has a big implication for them yes, absolutely so.

THE PRESIDENT: Let us take that example, so someone who has been seizure-free for two years, thinks they are on a stable regime, and the seizure happens. Their first port of call would be to where? Primary GP or would it be secondary or tertiary treatment?

A. So it depends -- so that depends on whether they are being followed up. Usually, what we would like to do is refer back patients to GPs who have been seizure-free. That does not always happen because some patients are very resistant to leaving us because they have been with us for so long and they are terrified of not having access to us.

If they are referred back to the GP then they will see the GP and the GP in those instances almost always refers straight back into our service.

THE PRESIDENT: Right, so that is very helpful, and do you mind if I unpack that a little bit? So when you have a patient who is on a regime, they will obviously be with a consultant like yourself, when one is stabilising the regime, but there is a stickiness even there in that the physician may be retained by the patient because they like continuity in their physician?

A. Yes, they do, and they get -- yes, there has been -- as I say, there has been sort of attempts and we are attempting at the moment because of waiting lists to try and discharge patients back to their GP who are well controlled. Some of the GPs do not like it because they are on drugs that they are not used to and not used to knowing how to manage those, so sometimes the GPs resist that and refer back in. Sometimes I get referrals back in even though the patient is still seizure-free because the patient has pressurised the GP to do that. So patients do like to have -- they do like to have this continuity of care, and they even get -- they get very upset if their consultant changes. So we, after some time, retire, and are replaced by somebody else and the initial thing is when you get somebody else's patients

is they are very upset because they have seen the same person for 20 years or so.

THE PRESIDENT: To be clear, there is a big advantage in that because you know the patient, you know what the notes mean, because you have written them?

A. Exactly, and, you know, when we have known how they have been over the years, we have recognised side effects that they may have had, adjustments that could be made, and so if you were thinking about optimum care, then that is what I would suggest, but it is just, you know, with pressures to service, we cannot do it.

THE PRESIDENT: It is a resource question, no, I do understand.

So the patient who has been stabilised and who is seizure-free, presumptively forever, I know that is not the case, but someone who has been seizure-free for two years, in that timeframe would they be going back to the consultant or to the GP with any frequency?

A. So they will be going back to the GP to get repeat prescriptions, although those now are done online, they will go back to the GP and the other thing that we would usually ask is that the GP carries out blood tests regularly.

So depending on what drug they are on, they may be every year or every three years, and we would ask for

those blood tests regularly.

THE PRESIDENT: So even in a stable patient without a seizure, there is some form of continued medical supervision, optimally at the GP level, but less optimally for your waiting lists sometimes at the consultant level?

A. Yes.

THE PRESIDENT: That is not just a question of getting the repeat prescription, although I can see that is necessary. You will have other tests which -- are they specific to the regime that will be carried out at regular intervals even in a stable patient?

A. Yes, there are, and those are again contained within the NICE guidelines. So, for example, vitamin D levels which I know I have gone on about, but, you know, osteoporosis is a growing concern for us, for all people on all anti-seizure medications and we will get those vitamin D levels done every three years, unless there are problems with the vitamin D and we may get them done more frequently.

THE PRESIDENT: So going back to our patient who has been seizure-free for a couple of years, and then has a seizure against expectation, the likelihood is, given the seriousness and the importance of stability, is that they will go and see a doctor?

A. They will, yes, sir.
THE PRESIDENT: It does not really matter who their first port of call is because it will either be you, a consultant, because they have retained that relationship, or it will be to a GP who will then refer the matter on to you because a seizure is very serious?
A. Yes.
THE PRESIDENT: So either which way, you are going to be back in the loop?
A. We get to see the patient again, yes.
THE PRESIDENT: Thank you. Given that there has been a seizure, you would be looking at a revisiting of the regime in that you would be saying: well, it clearly has not worked or does not appear to have worked, we therefore need to reconsider at least whether the regime needs to be changed?
A. So, yes, sir, that is mostly correct. What we would do is look to see whether there is any specific reason for the seizure, so it may well have been that the person has not taken their medication and Professor Sander mentioned that as actually a major cause. It may be that they have taken some other medication, and I have since seen that recently, so antibiotics, for example, can sometimes lower the seizure threshold, or they may have been ill or unwell. So we would look for other

reasons, we would look for reasons why they may have had that seizure, and those reasons that can be corrected. We would also do drug levels as well to see whether those have altered or fallen or changed, and we have a baseline for those, so we do a baseline when somebody is stable and then if they have a seizure then we can compare to that baseline.

THE PRESIDENT: So again, it goes back to the, you treat the patient as an individual, you do what is best for them.

A. Yes.

THE PRESIDENT: To what extent, at this stage, where something has clearly gone wrong, if I can use that in a very neutral way, a patient has had a seizure, you are looking into it, to what extent does physician preference in terms of moving for or against phenytoin come in? Let us take a situation where it does seem to us, having heard the evidence, that Professor Sander really does not like phenytoin and wants to move patients off and will, consistent with patient consent, take pretty much every opportunity to do so, we will put this to him and we will see what he says, but that is what we got from his teach-in, whereas your position is much more, if I may say so, conservative in that you want to keep a stable regime going on, and you would be inclined, if someone is on phenytoin, to keep them

there.

A. I would, yes. So certainly if they are seizure-free I would definitely want to be doing that. You know, many of the patients that I have seen who are on phenytoin, somebody else has tried to take them off and that is often why they end up being referred to me, but if they are stable, they are side-effect free, and they are managing well on their medication, then the risks for them of coming off, which would probably be about at least a 20% chance of having a seizure within the next year, even if they have been seizure-free for many years, will mean that -- I would obviously discuss with them longer term or potential side effects, but usually the reply is they would like to remain on what they are on.

THE PRESIDENT: I entirely understand. Of course, I am postulating a situation where something has gone wrong, because a seizure has occurred.

A. Yes.

THE PRESIDENT: Now let us suppose you, having spoken to the patient, discover that actually they have been a little bit naughty and they just have not taken their phenytoin, or indeed, all their anti-epilepsy drugs for a week or so, and that is the most likely cause of the seizure. Does the physician at that point have

medically proper ability to say: well, look, you obviously are not that attached to this regime, something has gone wrong, can I revisit the regime with you, we have got some better drugs now, why do you not try something different?

A. I think it depends on why the person has not taken the medication. You are absolutely right, if they had significant side effects or there was a reason why they were not taking them, then we would revisit the regime and say, right, what is the drug that is most likely to be causing the problem of which they are complaining, let us see if we can change that around.

Most instances, that is not the case. So the problem is that most people are quite poor at taking medication anyway, I mean, that is true of all of us, so if you have ever tried taking medication regularly, and if you are seizure-free, it is almost like you are taking a medication but you do not feel that you need it because you are not having seizures, and so there is an even greater propensity for people on anti-epileptic drugs not to take their medication, and so it is usually that, having a seizure, the wake-up call, and then they come and they are contrite, you know: I ran out -- usually it is they run out of their medication and they have been too lazy -- that is probably an unfair term,

they have not been able to get their medication from their GP, because they have not filled in the repeat prescription or it has been late or there has been delays from the pharmacy, and they have just not taken it for a week and that is usually what happens.

THE PRESIDENT: So let us take an instance where the patient has had a seizure and the presumptive cause is that they went on holiday for two weeks, they forgot their medicine and they just did not take it.

Now, there you would be saying there is no underlying problem with the efficacy of the regime, it is simply the failure to take the regime during those two weeks?

A. Yes, absolutely, and we could try and put in place something to improve their --

THE PRESIDENT: Their compliance, yes: do not forget your pills, that sort of thing. My question is this: I understand exactly why you would say: look, phenytoin has worked in the past, you have been X years seizure-free, we know why it did not work in this case, you did not take your medicine, let us just get you back on the regime and talk about, as you say, compliance, and that would be your position?

A. Yes, sir.

THE PRESIDENT: We will ask Professor Sander this, but if he

were to say: we have got an opportunity here, Mr X or Ms X, you are off the regime which has worked, because you have been on it a long time, changes have occurred in the medical process, I personally do not like phenytoin -- I, Professor Sander -- and why do we not try something else, because you are in a break now, there is a break in continuity, let us, with your consent, do something else.

Now, is that something -- I know you would not do that, but is that something which you would regard as a reasonable stance for a consultant to take in those particular circumstances?

A. It would be a reasonable stance, but the person would have to warn them that they may not get control immediately, so it is a stance that somebody could take. As you rightly say, by the time they have had one seizure, they are unable to drive. The other thing you would have to warn them against is that, you know, seizures are not without risk, and sudden and unexpected death in epilepsy, which occurs in about 1 in 500 people per year, is significant, with epilepsy, and if they are uncontrolled, then it is happening in about 1%, half to 1% of people.

So the risk you take is exposing someone to that risk of having further seizures, I would say to the

person: you have been well controlled on this, let us continue. Professor Sander may say: well, you know, there is the opportunity here to change. He would end up warning them about the risks that if they had continued seizures then, you know, that is something -- a risk that they are exposing themselves to.

THE PRESIDENT: Really it is a question of balancing two factors, and let me try and articulate them and see how far you agree.

One factor is the fact that in this example the regime has worked, and we know why it has not because they did not take their medicine. On the other side is the differing views, reasonably differing views, as to how pernicious, if I can be as tendentious as that, phenytoin is, and you had put to you a number of side effects and deleterious consequences of taking phenytoin, and you are of the view that actually phenytoin is not withstanding those side effects a beneficial drug that ought to be prescribed, particularly in this case, going forward, because it works.

A. Yes, sir.

THE PRESIDENT: Whereas, quite reasonably, one may take a different view about the weight of the pernicious nature of the phenytoin side effects and advise

a patient, of course informed consent is a prerequisite, but you would advise the patient that: here is an opportunity, I do not like phenytoin, speaking as a physician, let us try something else if you agree, and that is a perfectly reasonable alternative approach?

A. Yes, it is, sir, and I would say that -- and I am sure Professor Sander would do this -- that you would also take into account how many other drugs they have tried. If they have tried 20 drugs and phenytoin is the only drug to work, then you are going to be, you know, a brave person to say: right, let us try the 27th drug when you have something that has worked.

THE PRESIDENT: That is a perfectly fair point, thank you.

So that is the first category of, as it were, latent patient, patients who have been on a regime for some time, those who have had a seizure and we have dealt with that.

Move on to the next case, which is the instance where a patient is identifying side effects that either always were a problem and they are more sensitive to them or are getting worse for whatever reason. Now, in that instance, we do not have a seizure, we just have other problems. In those circumstances, the first port of call would be to the general practitioner, would that be right?

A. Yes, if they are -- well, if they are still under our care then they would come to us, but if they are not then the first port of call would be the general practitioner, and some of those side effects a general practitioner may deal with, but very often what they would do is then refer back in, it is exactly the same as before.

THE PRESIDENT: I see. So it very much would depend -- I mean, the ideal, as you have made clear, is because of resource allocation you would want them to go to the GP first and for the GP to exercise their judgment to refer or not?

A. Yes.

THE PRESIDENT: But it may not happen that way?

A. Yes, and one of the problems that occurs is that people will attribute side effects to whatever drugs they are on, or things to whatever they are on, but they may have some other reason for occurring, and the GPs are often quite good at screening those sorts of things out. For example, somebody may suddenly develop a rash, and they think: well, it must be the drugs that I am on, but it may have been a viral infection or some other infection. So the GPs can do that, and one of the challenges when we get referred back patients with side effects is to work out, one, whether they are due to the medication,

and then secondly, which medication, if they are on multiple ones, they are actually due to, and so those are judgments that we have to take.

THE PRESIDENT: I completely understand.

So assuming the GP in this case recognises that it is not an instance of a correlation without causation in other words, there is a sufficient risk of a causative link between the side effect and the epilepsy regime, what that GP will do is they will refer the patient on to their consultant?

A. Yes.

THE PRESIDENT: So same question as we had before. In that circumstance, where one has got a regime which is working in the case of seizures but is problematic in terms of side effects, your first port of call will be to tweak the regime to see if you can maintain the benefit of seizure-free periods whilst minimising the side effects?

A. It will be. That is usually the case. So most of the side effects that we referred on in that time are dose-related side effects, so they will be things like unsteadiness or dizziness, and then it is often a matter of just trying to reduce the medication to try and get rid of those side effects.

We would also do blood tests to look at what the

levels of the drugs are. So that is the approach that I think most of us would take.

THE PRESIDENT: I am grateful. To what extent would a patient in that situation -- in other words, seizure-free but materially concerned about side effects -- be open to a suggestion of regime change, in other words, a move away from, hypothetically speaking, phenytoin? I appreciate, of course, it depends on the individual patient, but as a general precept.

A. Yes, so I am sorry I cannot give a general answer here, sir. I mean, again, I can think of times where this has happened, so it is not -- you know, it is not an uncommon thing that we get referred in patients, and the problem would be, again, I can think of a patient referred in for precisely this problem who was on phenytoin, and the problem is that they had tried other medications and the reason why they were still on phenytoin was because it had been the only thing that had kept them seizure-free, and we had discussions about the side effects and so forth. They would not come off phenytoin. They would say: look, you know, I have my whole life, I would prefer just to reduce the dose and that is it, so that patient would be in that situation.

If, on the other hand, they have not tried much else and they are having side effects, then they may want to

change or may want to change on to a different regime, and, again, I can think of an example of that with the one person I have seen who actually had significant gum problems with phenytoin who had been on it, put on it as a first-line, actually, following head injury, and it was in recent times because he was put on it by a neurosurgeon, actually, but he was put on to phenytoin as first-line, it worked very, very well, and he was seizure-free, but he started to get these gum problems, and he was having considerable problems, and we had a discussion, he had not tried anything else and so we tried a different medication, and in fact, he was seizure-free on levetiracetam actually.

THE PRESIDENT: Of course it is very subjective, one can think of a number of factors; length of time you have been on a successful regime would militate staying on it.

A. It would, yes.

THE PRESIDENT: On the other hand, if you have been on a stable regime seizure-free for 10 years with no side effects, and the side effects suddenly appear, that might occasion a rethink; it depends on the patient's appetite for what they want by way of quality of life?

A. Yes, exactly, and what is important to them.

THE PRESIDENT: Going to the attitude of a physician, we

have discussed the range of different views that quite properly physicians might have, and I am of course assuming that no physician would do anything without informed consent from the patient, but to what extent does the fact that a patient has come in to the GP, been referred by the GP to the consultant regarding a side effect problem, present an opportunity to the physician who dislikes phenytoin to dislodge phenytoin from the regime and insert something else?

A. So, again, it would depend upon whether phenytoin was something that was the only thing that had controlled their seizures, where I think it would be prudent to keep them on phenytoin, but if phenytoin had been used early on in their treatment and there was an alternative, then it may be an opportunity to consider that, but you would have to again counsel them about the risk that they would have if they were seizure-free, they would have, you know, a significant risk of having seizures, and there has been a study, a study came out of Philadelphia, Mike Sperling, where I think it was about 20%, somebody can correct me if I am wrong, but I think it was about 20% of people changed from carbamazepine or phenytoin on to another drug had breakthrough seizures, so it is a risk that you take, and it may be that the side effects are severe enough

that you may want to change that person on to a different drug, and sometimes, again, we are mistaken in attributing those side effects to medication. This has happened to me recently, actually, not with phenytoin but with carbamazepine, somebody got referred in because they were unsteady on their feet, my immediate thought was, well, this is probably carbamazepine, we had a long discussion, it was unmanageable, and so I changed her to another drug, she had breakthrough seizures, it was a complete disaster, and not only that, when we changed to another drug, we discovered that her unsteadiness did not improve at all and it was due to something completely different, in fact she had a degenerative -- neurological degenerative disease as well.

So, yes, those are sort of judgments that we make, and, you know, those are risks that we will take, and those involved counselling, careful counselling of the patients we see, but I think -- I cannot emphasise enough really the importance of seizure-freedom. I mean, in terms of changes to quality of life, I think people think: well, you know, if it is a seizure once in a month, you know, how bad is that? I mean, for many people these just have completely devastating effects on their lives. They wander around just constantly

terrified that they are going to have a seizure and again, I see this, people who have been seizure-free for years and suddenly have a seizure, suddenly they are afraid to go to the supermarket, they are afraid to go out in case they have a seizure, it just has such a big psychological impact upon them, and sometimes people again -- sometimes people are not very good at predicting what it will be like if something were to happen to them. So they sometimes think: oh, you know, how bad would a seizure be? It is not until they have had the seizure that they suddenly realise, you know, what a devastating effect it has had on them psychologically and also socially in terms of being unable to drive.

THE PRESIDENT: If I may say so, what you are saying is that it is part of the physician's role to articulate as clearly as you have done the risks of attaching undue weight to the side effect that you are experiencing as against the seizure which in this scenario you are by definition not experiencing, and saying: be careful what you wish for, you may be able to get rid of the side effects, but if you move away from a phenytoin regime you may very well get that which you really do not want, which is a resumption of seizures?

A. Yes, you are absolutely right, and it involves quite

careful counselling of patients, and especially because, you know, there are patients out there for whom phenytoin is the only thing that is keeping them seizure-free. So you may want to take that risk, or they may want to take that risk, but we have to articulate that very carefully because of -- I think sometimes people -- people do not have sometimes a great grasp of risk. I mean, either in terms of percentages or in terms of what something will actually mean if it actually occurs to them, so we do have to explain that very carefully.

THE PRESIDENT: Again, there is a judgmental question and reasonable physicians could differ in terms of the weight that they would attach to being seizure-free and the weight they would attach to the side effects of a particular regimen in order to explain the situation to the patient before them?

A. Absolutely.

THE PRESIDENT: Yes.

A. I think, again, Professor Sander very rightly said this, you know, we get to the stage with people who are not seizure-free where they are willing to go and have bits of their brain cut out, bits of their brain cut out that will give them memory problems, bits of their brain -- I mean, I have had people who have been unable to work

following epilepsy surgery because of the impact it has had on them cognitively, but they are willing to take that risk to try and stop or get rid of the seizures.

I think it is sometimes very difficult to imagine what a life with seizures is like, but for many people it is absolutely devastating, and so we are willing to go to the extent of going in and doing brain surgery to try and get those people better.

THE PRESIDENT: I am grateful.

So moving on from the person who is seizure-free but suffering from side effects, second class, to the third and perhaps easiest class, which is the person who is both seizure-free and stable in the wider sense in that their side effects, whatever they are, are remaining constant.

I think we discussed earlier that that person would nevertheless be under regular GP care, it might be regular consultant care --

A. Yes.

THE PRESIDENT: -- but you would want to push them down to the GP level for all kinds of reasons, and that would be a form of care that would be more than just dispensing the repeat prescriptions: there will be blood tests, that sort of thing?

A. Yes, sir, and there will be -- and, I think as

I explained, I would take particular care and also emphasise the GP take particular care about cardiovascular risk factors, especially if they are on enzyme-inducing drugs which we know increase things like cholesterol.

THE PRESIDENT: So in combination the consultant and the GP would be liaising to make sure that they kept track that nothing was going wrong in terms of the patient's ongoing treatment?

A. Yes, sir, absolutely.

THE PRESIDENT: What might cause a GP to make a referral to a consultant in those circumstances? So I am postulating no seizures and no complaint by the patient that side effects were increasingly problematic, so as far as the patient is concerned, it is business as usual.

A. So when somebody is completely stable, the things that usually -- the reason people usually get referred is first of all, can they come off their medication, do they still require it, and so they get referred in to us to work out what is the probability of them being able to come off their medication successfully, or, I mean, that is probably the main reason why GPs would refer back in. If there are no side effects, no abnormal blood tests and the patient is tolerating the medication

well and they are seizure-free, then they would not get referred back in, and so the majority of those patients remain with their GP.

THE PRESIDENT: But if, for instance, a patient was suffering from some other form of malady, nothing to do with epilepsy, but it was being treated by some form of medication, in those circumstances a GP would be concerned about the interaction between the epilepsy treatment regime and this other new regime, and in those circumstances, would a referral upwards take place?

A. No, not usually. So if it is to do with drugs that manage blood pressure then they can monitor the blood pressure and titrate the drugs to get the blood pressure under control, and similarly with cholesterol, and those would be the main things that GPs would do.

If, for example, they get referred to -- they are unfortunate enough to develop cancer, they get referred to an oncology unit, the oncology unit will have experience of managing people who are on enzyme-inducing drugs, and so they will usually just manage the person without referral back to us.

THE PRESIDENT: It would be a brave, even a foolish GP, who would implement any kind of regime change off their own bat, that would not happen?

A. I can't think of when that has occurred, so they would

normally -- if they thought a regime change would be necessary, a regimen change would be necessary, then they would refer back to us, yes, sir.

THE PRESIDENT: So in this third class of case, unless there is something to specifically alert the general practitioner to the need to involve a consultant, the twin factors of no complaint about side effects and no seizures would mean that the process would be steady as she goes, one would simply carry on with the regime until the next GP consultation?

A. Yes, and I cannot speak for all GPs, but I think that is generally what happens. I think that, as I say, I do get referred in patients on all sorts of anti-seizure medications because they have been seizure-free for a long time and want to know whether they can come off their medication, and I think, again, you know, as we get older, we tend to accumulate medication and then people start to wonder why is it I am still on the phenytoin, I have been seizure-free for all this time and they want to know about the risks of coming off the medication so they will be referred back in.

THE PRESIDENT: Then finally, you mentioned a couple of times the significance of guidelines including guidelines from NICE. When it is, as a matter of prevailing wisdom, discovered that something is a bad

choice of drug, that is something which occurs at the general level and it is not something that either consultants or GPs need worry about. I mean, consultants no doubt are referring things into NICE, but you are not going to allow that to affect your general clinical judgment in terms of what you do and do not prescribe?

A. No, so, yes, you are right, the MHRA and NICE have important roles to play in providing national guidelines, and that if we were not to follow those guidelines, then we would have to have good reason to do so, and if I were, you know, standing in a court of law and something had happened, I would have to be able to explain why I had not used the guidelines that are generally accepted for physicians.

THE PRESIDENT: Professor, thank you very much.

I think Professor Waterson has some questions also.

PROFESSOR WATERSON: Yes, I do have a few questions.

One is are there particular sub-groups of people who appear to have different effects? In other words, just to give you an example, we know that South Asian people tend to suffer from vitamin D deficiency to a greater extent than Caucasian people. Have you noticed any particular sub-groups?

A. Yes, so there are differences in terms of racial

differences in responses to drugs, one you gave an example of, the other one is the risk of rash, for example, is much greater in Han Chinese than in Caucasians, and we also now know as sort of genetic test that we can actually use to try and predict that risk, and we use that with carbamazepine where it has a very strong correlation and there is now talk about using that as well for phenytoin.

So we have those particular things where we know that certain groups of people may be more susceptible to certain side effects, in particular, as I say, the allergy and the rash.

We also know that there are certain patients who may be more prone to certain side effects with drugs because of who they are. So, for example, people with severe head injuries who have, for example, psychiatric, severe psychiatric co-morbidities, we know that they may be much more prone to psychiatric consequences of starting certain drugs, and some of the drugs have more severe psychiatric consequences than others.

So for certain groups of patients we do have an idea of side effects that may be more prevalent in that population.

PROFESSOR WATERSON: So the second thing I wanted to ask you about is presumably you, and also Professor Sander, tend

to see what you might call problem cases?

A. Yes, I know it is a difficult term, but we see people with difficult to control epilepsy, complex epilepsy.

PROFESSOR WATERSON: So when you talked about referring -- people being referred to the tertiary level, that would not necessarily -- you would not necessarily be the first port of call: they might refer them to their local hospital, for example.

A. Yes, so the way that epilepsy services are divided, obviously there is GP and then there would be sort of general neurologists, which would be secondary care, and then there will be people who specialise in epilepsy which would be tertiary care, and then we are tertiary but also we are almost quaternary care as well, so when people have very difficult epilepsy who are seen by even epilepsy specialists elsewhere will sometimes refer in to us to try and improve the epilepsy control. So we see people referred from other specialist centres.

PROFESSOR WATERSON: So, for example, someone in, say, the Manchester area would be likely to be referred first to a hospital within the Manchester area?

A. Yes, I mean, the hospitals of Manchester are very good, actually, but, yes, I take what you say, and we do get referred patients down from Manchester.

PROFESSOR WATERSON: A third point. You talked about GPs

referring people back and so on. I think it would be reasonable to say that some GPs are better than others, some are more under pressure than others, some GP practices go for various reasons downhill over time, so you may not observe this, but do you think it is likely that there are some cases which should have been referred to you which never were because the GP says: oh, that is the problem with this drug, you just have to carry on taking it, you know, or they cannot get an appointment?

A. Yes, I am not going to answer your question, I am afraid I do not know is the answer to that question. I am sure there are patients in that situation, I do not know how many patients there are or what proportion, so I do not have that information to hand. I mean, I can tell you that I certainly know of patients who are seen by other neurologists who we would like to have been referred to our practice earlier, but I only know that because they are referred and then I would have said: well, I would have liked you to have been referred a few years earlier, but I cannot really speak to what is happening --

PROFESSOR WATERSON: Yes, like crime statistics --

A. Yes.

PROFESSOR WATERSON: -- you cannot tell about the prior

crimes that were never reported.

A. No, I cannot, so I am sorry I cannot answer that question.

PROFESSOR WATERSON: Finally, one thing that you did not mention, and I think I know the answer, but I am just checking, one thing that never crosses your mind in deciding on a regime for a patient is the relative costs of the various alternatives?

A. We -- it does and it does not. So, I mean, ideally what I like to do as a physician is to give whatever I think is going to be best for my patient. When drugs cost a considerable amount, then there are restrictions put on our practice, and then we are told about it, so I can give examples, so, for example, cannabidiol, which is all the rage, there are severe restrictions in our prescribing of it because it costs tens of thousands per year so we are told that we can only prescribe in certain instances and then we have to get permission. Cenobamate, where there are not such restrictions on it, the prescriptions at the moment are coming from the hospital because it has to come from specialist care, the hospital has come back to us and said: hold on, please calm down a bit with prescribing this new drug, it is costing us a lot of money, and so we do get that fed back to us.

So it does play some part in our prescribing. You know, I would like to live in that world where I can just prescribe whatever I think is best for the person in front of me, but sometimes I cannot and sometimes I am told that I should not.

PROFESSOR WATERSON: Thank you.

THE PRESIDENT: Just so that we have context, these are very much the exceptional cases: you do not have controls over cost in your prescribing practice?

A. No, so we do not -- so the prescribing tends to get -- tends to -- this is again a way in which things are influenced. The prescribing tends to go back down to the GPs. The GPs may well feed back to us and say: we are not happy to prescribe this drug, and that was something that was rare when Professor Sander and I were younger, but it is something that is becoming increasingly the case, so we will say, you know: we would recommend this drug, or: we would like to start the person on this drug and we would like you to continue it and then we get a message back saying: we are not going to do that, we are not happy to prescribe it, and then a whole debate ensues that we do not always win.

THE PRESIDENT: Just to be clear, I am sure we will be told by counsel anyway, there have not been any such controls

in relation to phenytoin that you are aware of?

A. No, not at all. The only thing that has at all affected phenytoin is what affected all drugs, which was again the reason why we have the MHRA guidance, was that there was a great move to the prescribing of generic formulations and that was mainly driven by the fact that, you know, levetiracetam and lamotrigine at the time cost about £2,000 per year, whilst generics were considerably cheaper, so there was a great push to go on to generic lamotrigine or, as Professor Sander said, parallel imports, he mentioned Portugal, I seem to see a lot of people where it came from Spain. So there was that sort of move to try and prescribe generics, and then there was a great upset amongst the epilepsy community, so patients got very upset by this, it was mainly driven by levetiracetam and lamotrigine. We wrote letters to the MHRA about this, there had already been guidance in NICE and then MHRA came out with this guidance and I have to say that, you know, the charities which I was very much involved with two, were very unhappy about this because it was really about lamotrigine and levetiracetam at the time. The MHRA took probably a logical approach, but they then divided into classes, because -- and that was -- they divided it into classes really because they wanted the generics to

be, I think -- I am not going to say what the MHRA wanted, but my reading of it at the time was that they wanted the generics to be prescribed for those other drugs. It was not really about phenytoin and carbamazepine and phenobarbital.

THE PRESIDENT: Ms Kerr Morrison, do you have any re-examination arising out of that?

MS MORRISON: No, thank you, sir.

THE PRESIDENT: No.

Mr Johnston?

MR JOHNSTON: No.

THE PRESIDENT: Professor, you are released from the witness box with our very considerable thanks. I know you have had to give up valuable working time to do this but I think you should be under no illusions, and the same goes for Professor Sander, of how useful you have been to us, thank you very much.

THE WITNESS: Thank you, sir.

THE PRESIDENT: Professor Sander.

MS MORRISON: Could I just ask Professor Sander to come back up and hand over to Mr Johnston.

PROFESSOR LEY SANDER (called)

Cross-examination by MR JOHNSTON

MR JOHNSTON: Professor Sander, I will let you reacquaint yourself with the box, make sure that you have got your

reports in front of you.

THE PRESIDENT: Yes, do work out what is in front of you and what you need. Do work out what is in be front of you in terms of papers and what you need. I think you have water. We are not going to re-swear you, Professor, because the oath you took this morning continues, and I will hand you over to counsel for some cross-examination.

A. I have here XE4?

MR JOHNSTON: Yes, that should contain your expert reports.

A. XE6?

Q. That should have your position statement in it as well.

A. Okay, I think that then I have ...

Q. Perfect. Professor Sander, can I start with some points that I hope will not be controversial so that we can lay some groundwork. The first of those is that uncontrolled epilepsy has very serious consequences for patients, does it not? You have nodded. If you could say "yes" that would be really helpful just for the transcriber --

A. Yes, I know, I think that that is a big issue, epilepsy carries a big burden, not only on people that have it, but of their families and society, and uncontrolled epilepsy is really a big burden, much more than controlled epilepsy, there is no doubt there is an

increased morbidity, people who have seizures end up injuring themselves, people may die as a result of a seizure at the wrong place at the wrong time, and there is something called sudden unexpected death in epilepsy, SUDEP, that takes about 1 in 100 to 200 people every year, and this is one of the reasons that epilepsy life expectancy is reduced, and it is even more the case in intractable epilepsy, chronic epilepsy.

Q. Professor Sander, that is very helpful, you have just answered my next four or five questions.

Professor Walker describes it as sort of being like the sword of Damocles hanging over the head of a patient and I think you agree with that, that is consistent with what you have just said?

A. Yes.

Q. If a patient has been seizure-free for a considerable period of time, an outbreak of uncontrolled epilepsy can be devastating for their quality of life, can it not?

A. Correct, yes.

Q. I would like to talk a little bit now about phenytoin. In a number of my questions, I would like you, if you can, to focus your answers on the state of the scientific knowledge and the state of your practice in the period 2012 to 2016, so I know I am slightly asking you to put yourself in a time machine, but if you can

orient yourself there, that would be extremely helpful.

Now, you have already said in your teach-in today and in your written evidence that phenytoin is an effective drug at treating epilepsy in some patients, is it not?

A. That is correct, yes.

Q. In 2012, I think you were here this morning, we heard that one in 10 anti-seizure medicines taken in the UK was phenytoin, was it not?

A. Yes, that is correct.

Q. If we could have on the screen before us {XA1/1/427}. Professor Sander, this is the CMA's Decision and they give a statistic there which is very similar to some we heard this morning:

"Notwithstanding this, approximately 57,500 patients in the UK were treated with Capsules in 2012..."

So there will be an additional number being treated with tablets in 2012. That is a considerable cohort of persons, is it not?

A. That is about 10% of the people with epilepsy.

Q. Yes. And continuing being treated on phenytoin is essential to maintaining their quality of life, is it not, that cohort of persons?

A. I think that if people are seizure-free and not having any problems as a result of the medication, that is

absolutely fine, that is how -- you know, there is no reason to change that, and you could argue it is essential for them to be seizure-free.

Q. Yes, that is how the CMA puts it at the end of this paragraph, do they not, they say:

"... ensuring a stable course of treatment is essential to maintaining their quality of life."

I think we are agreeing on that.

A. Yes.

Q. Your written evidence was that you had not prescribed phenytoin anew for the last ten years, but I was not sure whether you said this morning that there was actually one patient in the last year where you had.

A. I need to put this into context. What I said, I have not started a de novo patient --

Q. Yes.

A. -- probably, and I mean that when I see a patient in clinic for the first time that have been naive to anti-epileptic drugs, I probably would say it is even more than 20 years that I have not used phenytoin. However, I have on occasions, and I continue to do so where necessary, when I have no other option, to use this.

So it is not that -- we have now over 20 drugs, we need less and less people that reach the third line.

Q. Understood.
A. So this is why the numbers have gone down, and, as I explained this morning, we are seeing changes in the natural history of the conditions that led intractable epilepsy. There is an increased number of the elderly, so this is why we are having these demographic changes, and that is responsible probably for less chronic epilepsy these days.
Q. That is very helpful, thank you.
Now, you may not be able to assist the Tribunal fully with this if it is right that you have not prescribed phenytoin de novo for 20 years, but as well as that larger cohort of persons who were taking phenytoin in 2012 that we have just looked at, there was also a smaller cohort of persons for whom phenytoin could secure seizure-freedom when other drugs had not been able to achieve that result, was there not?
A. Yes, sir, that is the case, and I still think it is the case for a very small number of patients, where nothing has worked that may be phenytoin may be an option.
Q. You, I think said earlier in your teach-in, that you would expect in the third line efficacy to be at around 5%, is that right?
A. It was not me that said that, but I think that is about right, although there is a new drug that has just been

launched that has been mentioned, cenobamate, that this has gone up to about 30%, 40%, and --

Q. Thank you.

A. So this is a new option, and this is why, as Professor Walker said, we have seen this epidemic of prescribing this drug in this group of patients. Most of them will have had phenytoin already.

Q. That is very helpful. So just to orient ourselves back in 2012, before cenobamate has come on the scene which I think -- it is not on the scene in 2012, is it?

A. No, it came out after that.

Q. After that, so in 2012 we are talking in the third-line at around 5% of patients will respond to a third-line treatment such as phenytoin.

A. Yes.

Do you agree with me, I assume, that in 2012, NICE reviewed all of the evidence and recommended that neurologists consider phenytoin as a third-line treatment when other drugs have not worked, did they not?

A. Yes.

Q. That is because NICE of course assumed that phenytoin was going to work for some of those de novo patients, not the established patients, the guidance goes to the de novo patients and it is saying third-line phenytoin

should be started for some patients because it will be effective, does it not?

A. Well, maybe just to -- these patients would not be de novo patients because they already had treatment.

Q. Yes.

A. You could argue that they would be de novo patients for phenytoin.

Q. Absolutely, and that is a very helpful distinction because it is adjunctive therapy?

A. Yes.

Q. So they are not de novo, they are not walking into a clinic for the first time looking for their first ASM, but what the guidance says is de novo as regards phenytoin this is recommended, because it is going to work for some of these patients. Thank you.

Could we take a -- sorry, again, Professor Sander, it is being pointed out to me that --

A. I have, yes, correct.

Q. You have nodded, thank you, that is very helpful. Thank you, I know it is a slightly artificial dialogue and we all nod and give --

A. I will do my best, sir, to comply.

Q. We all nod and give all kinds of visual clues so I entirely understand and I will try to remind you if you have not done it.

Could we have on the screen, please, {XF4/3/119}.

I am sure this is very familiar to you, Professor Sander, this is the NICE guidance from 2012, and what we have in paragraph 1.9.3.1 is -- and this is looking at focal seizures:

"Offer carbamazepine or lamotrigine as [a] first-line treatment to children, young people and adults ..."

And then further down there is a discussion of second-line treatments, and if we could go to the bottom half of the page, we will see there that:

"If adjunctive treatment ... is ineffective or not tolerated, discuss with, or refer to, a tertiary epilepsy specialist. Other AEDs that may be considered by the tertiary epilepsy specialist are [I will not try to pronounce that one] ...lacosamide..."

A. Eslicarbazepine.

Q. And phenytoin appears in that list, but the first two drugs, if I can put it this way, off the shelf, were carbamazepine and lamotrigine in NICE's 2012 guidance for focal epilepsy. That is right, is it not?

A. Yes, carbamazepine was, yes.

Q. Could we have on the screen, please, {XF4/3/629}. Now, Professor Sander, are you familiar with this study? It is a Cochrane study from 2017.

A. Yes.
Q. It is a study of -- it is a network meta analysis. Now, you can probably explain that better than I can, but I will try and you can correct me, of monotherapies and epilepsy.

Firstly, are you familiar with the study?

A. Yes.
Q. It is right, is it not, that the Cochrane studies are regarded as kind of best in class because they are meta-studies, they look at all the other studies, they put them together and they try and amalgamate the data and make best sense of it?
A. I would not say that they are always the best, but I think that they have a reputation of doing good work.
Q. They are regarded as a high quality basis for informing clinical decision-making, are they not?
A. Yes.
Q. Thank you. What this study did was it compared various features of monotherapies by, as I say, looking at and conducting this study of studies.

Now, could we move forward within the document to page {XF4/3/656}, please. Now, this will take a little bit of unpacking. If we could zoom in on the bottom half of the screen that would be very helpful. Professor Sander, I do not doubt that you are more

familiar and more articulate than me in relation to precisely what this is describing, but let me try to describe it and then you can tell me if I have it right.

What we are looking at here is carbamazepine, so we are looking at the first-line treatment that I just described as first off the rack for focal epilepsy, and it is being measured against the other drugs in this study by reference to four metrics.

So if we start in the top left-hand corner, what we have there is everything to the left, CBZ worse, carbamazepine is not as good, everything to the right CBZ better, and then down the left-hand side we have lamotrigine, levetiracetam, valproate, I think that will be, zonisamide, oxcarbazepine, and if you look, phenytoin comes just beneath oxcarbazepine.

So what which have there in the top left-hand corner is time to withdrawal, so what we are looking at here is tolerability, how long will a patient stay on a particular drug, and you will see that carbamazepine has better tolerability than phenytoin. Phenytoin is 1.13. So help me if I am wrong, but my understanding of this is that what that means is, when comparing directly between phenytoin and carbamazepine, the first-line treatment, phenytoin does less well in terms of tolerability, patients are more likely to come off it.

Now, phenytoin -- sorry, I should give you an opportunity to answer rather than monologue at you. That is correct, is it not?

A. Well, yes, that is correct. However, I think that, you know, this is not head-to-head comparison, this is to some extent an artificial construct where you get the results of many different trials that were done at different times, and they are not head-to-head, so you need to take this with more than a pinch of salt.

Q. Well, I understand that as far as it goes, Professor Sander, but this is a Cochrane study, this is an attempt to put all of the studies together and best understand how we can assess efficacy and we will come on to that in a moment, and tolerability of all of these drugs. So if we see on the list lamotrigine, levetiracetam are better tolerated than carbamazepine, and, as we go down the list, phenytoin is by no means at the bottom of the list, it is above topiramate, it is above gabapentin, it is above phenobarbital, but certainly this study, which is a study of studies, says it is less well tolerated, not profoundly so, but less well tolerated. That is correct, is it not?

A. Yes, that is correct, that is right.

Q. Thank you. If we go to the right-hand side, this is time to 12-month remission. So this is the time, as

I understand it, that it takes for a patient to go 12 months without any seizures, and if we look at this table it is fair to say, is it not, that phenytoin is very, very close to carbamazepine in terms of efficacy, it is 1.03, it is not quite a rounding error, but it is very close. That is fair, is it not?

A. Yes.

Q. If we go to the bottom left, time to 6-month remission, we will find phenytoin again very, very close in terms of effectiveness to carbamazepine?

A. Yes.

Q. And if we go to the bottom right, we will find phenytoin very close again, but actually in this case, marginally better in terms of time to first seizure, the length of time to first seizure.

A. Yes. Could I just say, point out, that because the confidence intervals, they cross the line in the middle.

Q. Yes.

A. There is not really big difference there, they are not significant.

Q. Well, let me put this to you and see if we can agree. What we take from this is that when comparing phenytoin to the first-line drug for focal seizures recommended in the NICE 2012 guidelines, it performs pretty much the same in terms of effectiveness but is less well

tolerated. Would you accept that?

A. I would accept that, yes, in this situation.

Q. Thank you. Can we turn now to the next page, which is page {XF4/3/657}. This is figure 6, and hopefully this will be slightly more familiar or straightforward because we have seen a very similar table just a moment ago.

So this is comparing lamotrigine to the other drugs within this study. So again, just to orient ourselves again, lamotrigine is the other first off the rack treatment recommended for focal epilepsy. If we look at time to withdrawal, lamotrigine is, if I can put it in straightforward terms, better than everything, it is better tolerated that all of the products and again, phenytoin is just below halfway down, but it is markedly better than almost everything with the exception of levetiracetam.

If we then go to the right, so we are back into efficacy now, what we see in terms of time to 12-month remission is that phenytoin is not extraordinarily, but it is notably more effective than lamotrigine. That is right, is it not? It is at 0.89?

A. Yes, I take that.

Q. Then if we go down to 6-month remission, it is 0.92, so again, it is not a huge difference, but it is notably

more effective within the context of this study. That is right, is it not?

A. Yes.

Q. And if we go to time to first seizure, phenytoin is actually the second most effective drug within that context, and in that context it really is markedly more effective than lamotrigine?

A. Yes, that is correct, we heard this this morning already from Professor Walker.

Q. So again, what we take from this is that lamotrigine is better tolerated, patients are more likely to stay on it for longer, but it is actually less effective at preventing seizures than epilepsy within the context of this study?

A. Yes, it might be correct. I think that I have my concerns about this type of analysis, they are not head-to-head, but what I am trying to say here is that it is a package. You cannot separate efficacy from tolerability, they need to be taken together.

Q. Professor Sander, I am not going to shut you out and we are absolutely going to come back to those points, but if we can stick to this --

PROFESSOR WATERSON: Could I just raise a query, just to understand? These are box and whisker diagrams, are they, as far as you are aware?

A. Whatever you -- yes.

PROFESSOR WATERSON: So the box would be the 25 percentile and the 75 percentile I assume, but maybe that is wrong.

A. It is where it stays in the comparison and the line across, it is confidence intervals.

PROFESSOR WATERSON: Okay, yes.

A. Yes? So to be significant, different, the line in the middle, the confidence, should not cross the middle line.

PROFESSOR WATERSON: Right, yes. So, for example, in the table time to 6-month remission, you can say virtually nothing from that diagram?

A. Correct, yes, but you know, if you look at absolute numbers then you can -- that is correct.

PROFESSOR WATERSON: Yes.

MR JOHNSTON: It is fair to say, is it not, that the reason the Cochrane study is focusing on these first-line treatments is precisely to answer the question: these are the first-line treatments recommended by NICE, let us assess them, let us see where they fit, let us try to understand how effective are they by reference to other drugs, how well tolerated are they by reference to other drugs.

A. Yes.

Could we turn on to page {XF4/3/658} which is

figure 7. If we could zoom in again, so this is sodium valproate, so this is the first drug, to use my colloquial term, off the rack, for generalised epilepsy, and we see again when it comes to tolerability, lamotrigine marginally better, phenytoin, this time, slightly above half, but it is fair to say time to withdrawal less well tolerated, that is the top left quadrant, is it not? If you could say "yes", I am sorry, Professor Sander.

A. Yes, I am sorry, yes.

Q. I am very grateful. I know it is an artificial exercise in recording your views.

If we come to the top right, we see here phenytoin again is in this head-to-head study more effective than sodium valproate, is it not?

A. Yes.

Q. Not extraordinarily so?

A. Please let me -- it is not head-to-head, this is not a head-to-head study, this is a pooling of different studies and they have, you know, their problems.

Q. I --

A. Head-to-head when we talk is something else. This is when we compare, we do a study, for instance, comparing phenytoin against another drug. This is a pooling of different studies put together, so they are not

head-to-head. Thank you.

Q. You are absolutely right, it is not a single monotherapy trial head-to-head, what it is, is it is a collection of all of those monotherapy trials --

A. Yes.

Q. -- and all of the head-to-head trials put together to give us an overarching picture to give us the fullest picture we could possibly get, is it not?

So if we then go to the bottom left-hand corner, we will see phenytoin is actually the most effective in terms of time to 6-month remission, and it is again, not extraordinarily, but certainly notably more effective than valproate and likewise in time to first seizure. That is correct, is it not?

A. Yes.

Q. Could we now turn to page {XF4/3/633} of this study, and could we zoom in on the words "Key results". If you could read what is under "key results", and then I will ask you some questions, Professor Sander. (Pause)

A. Yes, read it.

Q. So what we take away from this is that phenytoin was at least as, if not more effective, than the first-line treatments recommended by NICE in 2012 at stopping seizures in this study, was it not?

A. Yes, and so was phenobarbital.

Q. So was phenobarbital, that is very helpful. I will come back to this at the end when we start to talk about the package, but I would like to move on now to talk about side effects.

Sir, I am conscious of the time. Shall I go for a few more minutes given that we have not got a hard stop at 4.15 at this point.

THE PRESIDENT: Yes, why do you not carry on until a convenient moment, thank you.

MR JOHNSTON: I am very grateful.

Professor Sander, shall we start with some things that I think from your teach-in and from your evidence we can agree on. The primary goal of epilepsy treatment is to prevent seizures with the least side effects possible, ideally no side effects?

A. Yes.

Q. But it is not always possible to treat patients in a way that gives rise to no side effects at all, is it?

A. I think that there is no such thing as a free dinner or a free lunch, and I think it is fair to say that every single drug that I know has side effects.

Q. That is very helpful. So every epilepsy patient has to pay for their lunch in some form. The question is how expensive?

A. No, that is not correct, because I think that it is

important that we remember that side effects are the exception, not a rule. With the exception of a few exceptions that we can actually predict when are -- the so-called acute, when you increase and you reach the ceiling with this drug.

Q. You are absolutely right and my question was imprecise. I think a much better way to put it is that all patients have to face the risk of paying for their lunch, albeit the risk may be different as between different drugs. Can we reflect it that way, or perhaps I am stretching the metaphor too far?

A. Yes, that will be correct.

Q. I am very grateful. So whether to use a particular drug is always a balancing exercise, and we have heard this already today: the patient and the doctor are weighing up the benefits, the risks, the upsides and the downsides of a drug. If you could say "yes" rather than nod --

A. Yes.

Q. -- that would be helpful --

A. Yes.

Q. -- I am sorry, Professor Sander, I am very grateful.

Now, there are different kinds of side effects associated with anti-seizure medications, are there not?

A. We have acute side effects, we have allergic

idiosyncratic side effects and we have the so-called chronic side effects.

Q. It is important to distinguish between those different kinds of side effects because they arise in different ways, and they can be addressed in different ways clinically, can they not?

A. That is correct, yes.

Q. So shall we start with acute side effects?

A. Yes.

Q. You have just explained them briefly, and I think we are agreed, they are related to the dose of an anti-seizure medicine in the blood, are they not?

A. That is correct, yes.

Q. Could we have on the screen {XF4/2}.

You may have seen this before, this is appendix 2 to Professor Walker's statement. It is a sort of table of side effects, and you did not say in your report responding to this that you disagreed profoundly with anything that was here, but tell me as we go if you do.

Could we turn to page {XF4/2/5}, please. So here we have the acute side effects of phenytoin and we have heard a bit about these already, so I can take this reasonably quickly: dizziness, drowsiness, nausea, diplopia, ataxia. Now, those are all unpleasant, are they not?

A. Correct, yes.
Q. But if they occur, they can be addressed in a number of different ways, can they not? The first thing that we heard from Professor Walker today was that he would titrate up the level of phenytoin slowly in order to head off the risk of these acute side effects before they happen?
A. This is the same for all drugs. No difference for phenytoin. I think that the problem I have with phenytoin in this regard is that the gap between the poison and the good effect is very short, and sometimes a tiny increase in the dose can cause -- you know, with other drugs, it is a slow process, but with this drug sometimes it is quite an acute process.
Q. Well, let us take that slowly, shall we, because Professor Walker's evidence was -- and I think you are agreeing with him -- that you can go, as with all anti-seizure medicines, a long way to mitigating the risk of acute side effects by slowly increasing the drug, and he gave the example of a patient who is on 25mg one day but not the next day, and then maybe you would add in 25mg daily. So you can, and you do clinically build this up slowly to mitigate these risks, do you not?
A. Yes, my question back to you is why would you do it if

you have other options that are not so complicated?

Q. Well, Professor Sander, I do not mean this disrespectfully at all, but the process is that I ask the questions, you have had an opportunity to do a teach-in.

A. Fair enough, yes, I am sorry for --

Q. It is absolutely fine, but I will ask the questions and, as I say, you have had a full opportunity to do a very helpful teach-in.

So the process of building up slowly and then ultimately if these acute side effects manifest themselves, as you say with phenytoin or with any drug, you would then reduce and potentially even stop and try something else. That is right, is it not?

A. That is correct.

Q. Now, on the same page, so we do not need to turn anywhere, we have pregabalin, which is a much newer anti-seizure medicine from 2004, and it is another, in fact, third-line treatment for focal seizures, is it not?

A. Correct, but I must make a disclaimer here. I do not use this drug because it does not work. You know, it is a surprise because its main use these days is as analgesic, and I think it works when someone has anxiety, which is another indication. So I must say

here that I hardly ever use this drug. When I use it, it is for co-morbidity.

Q. Okay, well, I will take another drug, then, on that basis. Can we turn to page {XF4/2/6}, please. So here we have valproate, this was the first-line drug first off the rack for generalised seizures. So this is a drug that back in 2012 you would have been using, is it not?

A. Yes.

Q. If we look at the acute side effects there we have nausea, vomiting, hair loss, easy bruising, tremor, weight gain, obesity and dizziness.

A. Correct, yes.

Q. Again, that is a list of serious and unpleasant acute side effects, is it not?

A. That is correct, yes.

Q. Could we turn to topiramate which we will find on page {XF4/2/7}. Now, I think this is the drug that Professor Sander was referring to --

A. Professor Walker.

Q. Professor Walker, rather, I am very grateful -- as causing word-losing problems which might be every barrister's worst nightmare, but if we look at topiramate: cognitive impairment, weight loss, sedation, paraesthesia, fatigue, dizziness, depression. So again

we have here with a second-line treatment a serious substantial list of acute side effects, do we not?

A. Yes, that is correct, and I was the person that described the cognitive impairment, so I know all about this, and it is not a pleasant drug.

Q. So there is nothing unusual about the acute side effects of phenytoin as compared to a number of other products that were first or second line in 2012, is there?

A. This is correct if you look at the list, but I think that the issue, as I said, is that it turns up their phase much quicker if you are reaching the point of saturation. So that is a difference, because this is the only drug that we have that does not have a clear linear kinetic, so --

Q. That is very helpful. So the difference, if I can capture it this way, as regards acute side effects is not as regards the side effects; it is the non-linear pharmacokinetics, he said garbling the word?

A. Yes.

Q. I am very grateful. Could we turn now to idiosyncratic side effects. Now, I think you have already explained today, idiosyncratic side effects, they are akin to allergic reactions, are they not?

A. Correct, although sometimes they are not straight -- strictly-speaking allergic, for instance on topiramate,

an acute red eye is not an allergic process.

Q. No, that is very helpful. So perhaps a better way to put it is whilst they are not all allergic they are things that arise -- and see if you are with me on both of these things -- firstly, infrequently and secondly, quickly, if I can put it that way?

A. Yes, and not expected, I would say that these are side effects that you do not expect when you start.

Q. Yes, I am very grateful. Could we go back to phenytoin on page {XF4/2/5}. So we have here rash, Stevens-Johnson Syndrome, and we have heard a little about that, that is the very serious side effect that particularly affects Han Chinese patients. That is right, is it not?

A. If they take carbamazepine, not phenytoin.

Q. Not if they take phenytoin, I am very grateful. Hepatic failure, dermatitis, rash, agranulocytosis and lymphadenopathy.

So those are the idiosyncratic side effects of phenytoin, and if you had a patient that demonstrated even the beginnings of any of these, you would take them off that drug immediately, would you not?

A. That is correct, yes.

Q. Could we turn to valproate now, which is back on page {XF4/2/6}. So again, this is the first drug off the

rack, unless you are a woman of childbearing age, as I understand it, in 2012, for generalised epilepsy, and we look at the idiosyncratic side effects here, we have agranulocytosis, which we have just seen for phenytoin, Stevens-Johnson Syndrome, same again, aplastic anaemia, thrombocytopenia, hepatitic failure, pancreatitis and immune problems?

A. They are similar, but I think that again there is a disclaimer here on behalf of valproate. Most of these idiosyncratic side effects, they tend to occur in young age, particularly below the age of two years, so they are rarer, much rarer in adults.

Q. That is helpful.

Could we turn to carbamazepine now which is on page {XF4/2/1}. So again, carbamazepine, first-line treatment for generalised epilepsy: rash, Stevens-Johnson Syndrome, bone marrow suppression, aplastic anaemia. So again, that is a very serious list of idiosyncratic side effects?

A. Correct, yes, I agree.

Q. Looking at these lists, again, there is nothing unusual or outlying about the idiosyncratic side effects of phenytoin sodium, is there? They are comparable to other drugs recommended as first or second-line treatments by NICE in 2012?

A. Yes, that is correct, yes, I would agree with that.
Q. Shall we move on now to chronic side effects?
A. Yes.
Q. So chronic side effects are those that emerge after taking a drug for a long time, in some cases even for decades, are they not?
A. Yes.
Q. Phenytoin is one of the oldest anti-seizure medicines?
A. Yes, it is a pair of German drugs from the 1930s or before, phenobarbital.
Q. We know, it is fair to say, more about the chronic side effects of phenytoin than other newer drugs because it has been around for longer, has it not?
A. That is correct, yes, it has been around for longer.
Q. Could I ask if we could have on the screen {XG/449/1}. If we could go to page {XG/449/3} and paragraph 16, if you could just read that, Professor Sander. (Pause)
A. Yes.
Q. Now, I am very sorry, I should have explained to you what this document is before I leapt in to --
A. I know what it is, thank you.
Q. It is the note of your minute of your meeting with the CMA in November 2020. So what you are explaining here to the CMA is that the chronic side effects of anti-seizure medicines sometimes only become clear after

many years, as we have just discussed.

A. Yes.

Q. So we know more about the chronic side effects of older drugs, and there therefore will be some risk for patients attached to trying newer drugs, and that is what you are saying in the final part of this sentence:

"... therefore they will want to try new drugs despite the risks."

A. Correct, yes.

Q. Your view has not changed in that respect, has it?

A. No.

Q. Could we turn now to {F4/11} and to page {F4/11/1}. Professor Sander, I am confident you know what this document is because it is a document that you co-authored?

A. Yes.

Q. With a co-author whose name I will not brave because I am sure I would mangle it.

A. Athanasios Gaitatzis.

Q. Thank you, that is very helpful indeed. This is a study from 2013, as I recall. I am not sure if the number 2013 is on the first page, could we go to the second page {F4/11/2}. No, no joy there. Could we have the third page {F4/11/3}. There we go. So published online 15 May 2013. What this is, is a study that looks

at and addresses the topic of the long-term safety of anti-epileptic drugs, does it not?

A. Yes.

Q. If we could go halfway down -- sorry, I am crouching slightly to get closer to the screen -- halfway down the page in the left-hand column there is a sentence that starts:

"While physicians ..."

Can you see it? It is about eight to ten lines up from the bottom of the page:

"While physicians are aware of ..."

Can you see that?

A. Yes.

Q. If you could just read that to yourself, that would be great.

A. Mm-hmm. (Pause)

Yes.

Q. So again, that is just reflecting what you said to the CMA in 2021, is it not, about the importance of recognising that long-term side effects can take years to become clear?

A. Yes, but I am not saying that they have chronic side effects. I am saying that these are drugs that we do not know much about, that is what.

Q. Precisely so, thank you, that is a helpful

clarification. Shall we start by talking just a bit about chronic adverse effects in general.

So sticking with this study, if we go to page {F4/11/4} and to the left-hand column if we could zoom in just about halfway down. Now, Professor Sander, this is a very distinguished study, it has so many footnotes in that I am going to largely orient you by the footnotes to find the sentences I am taking you to, but obviously please read the context, but just after footnote 18, which is helpfully in blue, there is a sentence that starts:

"In the ..."

If you could just read that. (Pause)

Just help me to make sure that I have understood this correctly. What that is saying is that almost 50% of patients who start on an anti-epileptic drug will experience unacceptable side effects. That is right, is it not, of some form?

A. Of some form, yes.

Q. And that around 20% of patients discontinued their treatment because of adverse effects?

A. Yes.

Q. And that half of those happen pretty soon, actually, within the first three months of taking --

A. That is commonly the case, still in practice. That is

when people discontinue it earlier on.

Q. So what we take from this is that adverse effects for anti-seizure medicines are pretty common, they are routine, are they not?

A. It depends on -- I think that if we were to look at the specific drugs, there is going to be a range: some drugs are better tolerated than others.

Q. Precisely so, and we saw that to some extent earlier, and more than half of those patients who experience some adverse effects stay on the drug anyway. So the figures you have here -- and I recognise that they may be rounded, but 50% face an adverse effect, 20% come off the drug as a consequence, and if they stop taking it, they do it pretty quickly, within three months or so. If we could just read right on to the end of the next two sentences which you may have read before, I am not sure, but if could read to the end of the paragraph.

A. Yes.

Q. One of the things it is saying there is that those drugs that have high retention rates are more likely to be associated with high levels of adverse effects in the longer term and the simple point there is: if you are on the drug for a long period of time, you will see high levels of adverse effects. That is right, is it not?

A. That is correct, all sorts of things can happen over

time.

MR JOHNSTON: Sir, I think that might be a convenient point. I am mindful of the time. I anticipate that you will have some questions for Professor Sander, I have obviously considerably more, but I am making reasonable progress if that helps you in terms of timing and I am mindful the shorthand writer had a short lunch.

THE PRESIDENT: Yes, we will certainly take a break now since that is a convenient time. We will resume at 3.30 and we will go on, I think, until 5.00, I think we will need some persuading to go longer than that.

(3.20 pm)

(A short break)

(3.36 pm)

THE PRESIDENT: Mr Johnston, good afternoon.

MR JOHNSTON: Good afternoon.

Professor Sander, we were looking just before the break at your 2013 study of long term safety of anti-epileptic drugs and on page 5 and page 6 of that study you have a very useful table if we could turn that up now. Not to zoom in for now, but table 2 {F4/11/5}, "Clinically important late aide of anti-epileptic drugs". So what we have here down the left-hand side is a whole series of adverse effects, and then on the right we have whether or not different AEDs are associated

with them, do we not?

A. Correct.

Q. Now, I have read your study very closely, you will be pleased to know, and I got my highlighters out and did a bit of my homework and counted up the number of times that phenytoin is associated with a late adverse effect in this table.

Now, recognising that there is something at least slightly impressionistic about that, on my count, phenytoin is associated with an adverse effect in this table, which is page {F4/11/5} and {F4/11/6} 21 times. Now I am happy to be corrected if I have slightly miscounted but I think that is in the ballpark. Does that sounds about right to you having done the study?

A. I have not counted, but I can count if you wish me to.

Q. I think probably rather than count them --

THE PRESIDENT: I think if there is an error that is material, then somebody will correct you --

MR JOHNSTON: Yes, exactly so.

THE PRESIDENT: -- we do not require the Professor to count the references.

MR JOHNSTON: But I hope that sounds at least about right to you, Professor Sander?

A. Yes.

Q. It is also right to say that carbamazepine, so that

first drug off the rack that we were talking about earlier, is included in this list 22 times, so phenytoin 21 times, carbamazepine 22 times.

Now, carbamazepine was the first-line drug recommended by NICE in 2012 for focal epilepsy. As I say, I am not expecting you to do the maths on the spot, but is it fair to say in your study from 2013 that it is associated with the same volume of adverse effects?

A. Both are enzyme inducers and therefore it is not a surprise, because many of these chronic side effects will be arising from its enzyme-inducing properties.

Q. We are going to come to enzyme induction in a moment, just so you are --

A. Yes, and probably if you count phenytoin -- phenobarbital, it will be also high.

Q. So the other drug I counted up was sodium valproate which is another of the first-line drugs first off the shelf from 2012. Now that is included in this list, again, 22 times, so one more than phenytoin, the same number as carbamazepine, and that is not an enzyme inducer, but it is in fact an enzyme suppresser?

A. A blocker, yes.

Q. Blocker, yes.

A. But they modulate enzymes one way or another.

Q. Yes.
A. They are not exactly the same, but --
Q. But enzyme-effecting in some way, albeit via a different mechanism, is that fair? One is inducing, the other is blocking? That is helpful.

Now, to be fair, some of the newer drugs in this table are associated with fewer side effects. So oxcarbazepine, on my count has only five, levetiracetam does even better with three, and lamotrigine has four. Is that at least roughly consistent with what you would expect from this table? I recognise that you have not had a chance to go through it with a highlighter as I have and count them up?

A. Yes, I think that it is about right, and I think that you -- in this sort of situation where you are doing this, you go with a magnifying glass to make sure that everything is picked up, but again, you know, you need to remember that you cannot always compare things directly head-to-head.
Q. Indeed, and we will come to that. So can I also clarify this, that certain items are in bold in your table, so if we look at the very top line:

"Skin and cosmetic. Alopaecia, hair loss/thinning."

Valproate is in bold and what that means according to the footnote is that it is particularly associated

with that adverse side effect?

A. Yes, with hair loss, yes.

Q. So again, I have done the maths on this, and tell me if you think this is outside of the ballpark of what you would expect, I find phenytoin strongly associated with an adverse effect eight times, carbamazepine, the first drug off the rack for focal epilepsy, nine times, and valproate, the first drug off the rack for generalised epilepsy, twelve times. Is that roughly about right?

A. That is probably right. I have not counted, but I would not dispute it.

Q. So what we can take from that is as of 2013, consistent with this study, carbamazepine and valproate were strongly associated in this report with more adverse effects than phenytoin?

A. Correct.

Q. If we could go over the page to page {F4/11/6}, we will see here that as I said earlier, some of the newer drugs are also strongly associated with certain adverse effects, so if we look at, in the psychiatric category, anxiety, both lamotrigine and levetiracetam strongly associated with anxiety, irritability and agitation, again, levetiracetam there, and psychosis, levetiracetam again.

So even the newer drugs are strongly associated with

some adverse effects, are they not?

A. Well, let us put this into context. It does not mean strongly in terms of numbers, it just means that they can happen and they can be strong. That is basically what I think that this means.

Q. If we look just at the bottom of the table, it said: "Bold font indicates AEDs that are more frequently associated with a particular [adverse effect]."

A. Yes.

Q. So what it is saying is: these are the AEDs that are more regularly associated, the others will be to a lesser extent, but if you want to know which AED is most heavily associated with psychosis, for example, then you would say levetiracetam is on that list, but not topiramate, for example?

A. Correct, yes, but this was in 2013.

Q. Yes.

A. Yes.

Q. So what we can take from this is that phenytoin is not an outlier in terms of the range of clinically important, late adverse effects associated with it, by comparison to some of the first-line drugs recommended by NICE in 2012: valproate, carbamazepine?

A. That is correct, yes. That is what it suggests.

Q. Can we talk just a little bit about some of the

conditions that are unique to phenytoin. You will see within the table that there are a number of conditions that are unique to particular drugs, but there are three that I have found that were unique to phenytoin. If we could go back to page {F4/11/5}, the first of those quite near the top is gum hypertrophy. This was something Professor Walker was addressing this morning and his evidence was that gum hypertrophy can be addressed in most cases by good oral hygiene. You do not disagree with that, do you?

A. It can sometimes, like many things. I must -- I think that Professor Walker did mention that I would not be the best person to discuss phenytoin because I hardly use it, and so I have not seen it recently, but I have seen many cases of gum hypertrophy. I had cases where unfortunately the person could not come off phenytoin, and a dentist had to do procedures on the gum. So I think that it is not as uncommon, and I would say that probably one in four have gum hypertrophy if you go to doses near to the sort of therapeutic range.

Q. That is very helpful. Could we go to your position statement to {XE6/9/5}, paragraph 23. In the middle of that paragraph:

"Gum hypertrophy or swelling affects well over two-thirds of people taking phenytoin for more than

a few months and leads to damaging oral hygiene issues."

Can I just clarify that your evidence today is that it is probably not as high as two-thirds, is that right?

A. No, no, I would say that depending on how you count, if you ask people on phenytoin if they have bleeding gums, quite a lot of people will say that. If you now look for the evidence of gum hypertrophy it will be less, but gum problems is an issue.

Q. Just so I am clear, because I am trying to make sure we have got a full picture: your evidence is here gum hypertrophy or swelling affects well over two-thirds of people, so we are talking up into the 70s or plus per cent of people, but actually what you are saying is it is more nuanced than that, you are saying that some gum effect may affect a larger proportion of people?

A. Yes.

Q. But the gum overgrowth and other things that Professor Walker was talking about, that is a considerably smaller subset. Is that what you are saying?

A. That is correct, but my view is that if you go to doses that are near the threshold, then you are probably going to see more.

Q. Shall we go back to the 2013 study, so to {XF4/11} and page {XF4/11/7}.

So if we go into that second paragraph, just after the footnote, and slightly confusingly there are two footnote 35s, but it is the second footnote 35 I am looking at that starts:

"Chronic PHT treatment ..."

I might read this because it is brief:

"Chronic PHT treatment may also result in gingival hyperplasia ..."

Which is what we have just been talking about, overgrowth?

A. Yes.

Q. "... in 10-40% of people."

So it is fair to say that your assessment in 2013 is that we are in the lower end, we are in the sort of 10% to 40%, consistent with what you said just now, maybe one in four, is that fair?

A. That is correct, yes.

Q. If we go on to read the next couple of sentences:

"People with poor oral hygiene are at higher risk and, therefore, good dental care is important in people receiving PHT. Most studies found a dose-related effect of [phenytoin] on the severity of gingival hyperplasia [and] some showed no such correlation. The mechanism of gingival hyperplasia is multi-factorial and incompletely understood. It has been postulated that it is due to

the stimulating effect of [phenytoin] on the inflammatory response in individuals with chronic gingivitis..."

And so on and so forth. So what you are saying there is consistent with what Professor Walker said today which is that good dental hygiene is a very important means by which to mitigate this, is it not?

A. This is correct for all of us, good oral hygiene is very important.

Q. I am sure we can all agree on that, Professor Sander. We have an outbreak of confident agreement around the court.

Shall we look briefly, if we can go back to page {XF4/11/5} within this study, and, as I say, I do not want to create a false impression, phenytoin is uniquely associated with three adverse effects. There are a number of other drugs that are too, but I am not going to go through all of those. The second is neuropathy, so that is right at the bottom of the page there, can you see, neuropathy there?

A. Yes.

Q. That is broadly understood nerve cell damage and it can take -- manifest itself in different ways, is that right? If we could go now to {F4/11/11} so within the same document, and just under 2.11, if you could read

that paragraph, Professor Sander, that would be helpful. (Pause)

A. Yes.

Q. If we could just go over the page as well {F4/11/12}, just read to the end of the paragraph. (Pause)

So what we take from your study in 2013 is that chronic use of phenytoin, to use your words, may be associated with mild, usually asymptomatic, sensory motor neuropathy. So it is uncertain at best; is that fair?

A. I think that for some people it is very clear that there is no other explanation for neuropathies, and actually, it is not uncommon, for I have had referrals to my clinic, and we even shared -- I shared a case with Professor Walker where someone was referred to come off phenytoin because of a neuropathy of unknown origin, and this lady, I think there is no other explanation for her neuropathy. Probably I would say that the physiopathology of this is not very clear, but there is definitely something there, where it is mostly (inaudible).

Q. Can I just test that, Professor Sander, because you said there is definitely something there, but your study from 2013, if we can go back a page {F4/11/11}, did not put it any higher than that it may be associated -- and this

is a study gathering all of the evidence at the time, so is it that your opinion has changed between 2013 and now?

A. I think that it has changed since, this is ten years on, life is a dynamic process, we see more people, and you get to know more, and I think that I would not be able to explain it, but definitely there is something there as there is some people that dispute if there is a cerebellar atrophy with phenytoin, I think that the jury is still out, but we see this in clinic. Not that long ago I saw a gentleman that clearly, over a year and a half on a high dose of phenytoin developed cerebellar atrophy, and he had to come down on the dose to save that. I do not know how to explain it apart from the fact that this person was taking high dose of phenytoin.

Q. So just to take that one step further for a moment, what you are saying is where adverse effects of this kind arise, what you would do -- the first thing you would do is to reduce the dose and see if that mitigates the adverse effect?

A. Yes.

Q. Just to test just briefly -- and you have been very fair and said the state of the science has changed, this was the position in 2013, I think that is what you are telling us. It also says in your study here that it is

normally asymptomatic. That is certainly your evidence from then -- not your evidence, that is not fair, that was certainly your opinion then.

A. Yes.

Q. Has your opinion on that changed at all?

A. I think that definitely has changed. It is not -- I think that what we do not have, and I do not know the evidence if it exists, is actually a study looking at nerve conduction and people taking this drug. You know, sometimes people come and tell that they have some paraesthesias and things and then you test and they might fluctuate, they might go, but it is definitely more common with people taking phenytoin than other anti-epileptic medications.

Q. Can I just clarify, Professor Sander, when the CMA approached you in the course of its investigation and when the CMA approached you in the context of this appeal, they did not ask you to contextualise your evidence by reference to the state of the knowledge in 2012 to 2016, did they? You were asked for your opinion on phenytoin, if I can put it that way.

A. I must say I don't remember exactly, but it was pointed out repeated times that this referred to the period of 2012-2016, but I do not recall exactly how our conversation started, so --

Q. That is fair.
A. -- that goes back probably more than a year.
Q. The only other adverse effect that is uniquely associated with phenytoin is IGA deficiency which I think we will find on page {F4/11/6}. I think we will find it on page 6. Maybe it is on page {F4/11/5}. Here you go, yes, my apologies:

"Immunological. IgA deficiency."

If we can go to {F4/11/10} and paragraph 2.6, immunological. If you could read that, Professor Sander. (Pause)

A. Yes, I have read it.
Q. What you are saying there is whether or not this has any clinical significance as of the state of clinical knowledge in 2013, was not known. That is right, is it not?
A. I think that we are still there.
Q. Right, that is very helpful. It is fair to say, and I will deal with this reasonably briefly, that some of the other first-line or leading AEDs were also the only drug associated with serious adverse effects. If we could go back to page {F4/11/5}. So valproate, and again, I know I keep saying this but I want to keep this at the front of our minds, first drug off the rack for generalised epilepsy, is the only drug I read in here

associated with polycystic ovarian syndrome, metabolic syndrome, pancreatitis, this one I think might defeat me, thrombocytopenia/anaemia. Those are all unique to valproate and all serious side effects in their own right, are they not?

A. Correct.

Q. Carbamazepine is not associated with anything on its own, but it is one of only two associated with hyponatremia?

A. Correct. The other one is oxcarbazepine and now there is a third drug called eslicarbazepine that can be significant hyponatremia. In older people it could as high as 40%, 50%.

Q. Could we turn now to page {F4/11/16} within this study? This is your conclusion:

"The long-term safety of AEDs primarily depends on their effectiveness and their systemic and metabolic effects. The newer AEDs appear to be associated with fewer late or chronic AEs than the old AEDs, although greater use and more experience over the years, as well as more prudent use of the old AEDs, may change this perception. Future advances in pharmacogenomics and understanding of AED CNS and systemic actions [may] help prevent and minimise late AED AEs."

That is your conclusion regarding the overall

picture of adverse effects in 2013, is it not?

A. Yes.

Q. Professor Sander, can I put some propositions to you and see if you agree with them.

First, at least as of the time of your 2013 study, all of the AEDs you looked at were associated with at least some chronic side effects?

A. Correct, yes.

Q. That included the newer first-line drugs like lamotrigine and levetiracetam, albeit fewer in their case?

A. I think that looking back now you would -- not quite sure if I would describe them as chronic nowadays.

Q. Right.

A. For instance, the anxiety you sometimes see the psychiatric problems with levetiracetam that we heard, they might be an iatrogenic reaction in some people, because some of the psychiatric side effects of levetiracetam you may see quite earlier on.

Q. Yes, albeit you have captured them here in that category, that is fair, is it not?

A. Yes.

Q. As of 2013?

A. Yes.

Q. And the chronic side effect profile of phenytoin was not

markedly different from that of carbamazepine, an older first-line drug?

A. Well, you know, there is two ways of looking at this. Let us put it the way: intensity probably was not the same as some other drugs, but I put my hands up, some chronic side effects of some new drugs we might not know, they might take years to come out, but I think that what we have different nowadays is pharmacovigilance which is much better and that allows us to pick up some chronic side effects like Professor Walker mentioned already. Vigabatrin took seven years, Retigabine took three and a half years for the first reports. Felbamate was very quickly, eight months. Progabide was another drug that was picked up within two years.

So I think that the side effect, for instance, of phenytoin, like chronic side effects of phenytoin were already described in the 1950s.

Q. Yes, well, fully.

A. So it is actually, I think, a question of time.

We are much more attuned to look for side effects in new drugs because of the fact that we have this than we were maybe 20, 30 years ago.

Q. Yes, that is very helpful. The just to come back to the question I put, because I just want to make sure that

you have had a fair opportunity to answer it and a full picture. So the chronic side effect profile of phenytoin in this study from 2013 was not markedly different from that of carbamazepine, was it?

A. Yes, both enzyme inducers, so you should not expect any big difference.

Q. And the chronic side effect profile of phenytoin was not markedly different from that of valproate either, was it?

A. It was different, yes, but you have problems.

Q. Well, it was not markedly different, we have seen that it is associated with a similar number --

A. Yes.

Q. -- and that actually valproate was associated with considerably more. This is the drug which produces this in the greatest numbers, was it not?

A. Yes.

Q. Can I take you to your position paper, please, at {XE6/9/9} and paragraph 36.

The first sentence of paragraph 36 says:

"In my view, it is impossible to beat phenytoin as the drug with the most side effects in number and potential severity, and these are mainly long-term effects."

Now, is it right to say that this answer reflects

your views now because it is not consistent with what we have just been discussing about your study from 2013?

A. I think that what -- you could argue what is not in that paper, that was a listing, but I think the severity is something different, and I stand by what I wrote on paragraph 36. Now, I would have problems, I admit, to say how strong I was with this in 2013 than I am nowadays.

Q. So what you are saying, I think, is you accept that the position in 2013, at least, was that it was not associated with the most side effects in number, but you may be saying that you think the potential severity of those, your evidence is would have been greater in association with phenytoin?

A. Yes.

Q. Even though when we have looked at drugs like carbamazepine and valproate we have seen that they are associated and in some cases uniquely associated with some very serious side effects?

A. Yes, but again, I go back to the enzyme inducing.

Q. But carbamazepine is enzyme inducing as well, is it not, Professor Sander?

A. Yes.

Q. But that is the first drug off the rack in 2012?

A. Yes.

Q. I am suggesting to you that both in terms of number and severity, the side effects associated with carbamazepine are similar to those of phenytoin by reference to your study from 2013?

A. Yes, I think that that would be correct in that context.

Q. In terms of valproate, I think the same would apply, would it not?

A. Yes, if ...

Q. Now, if we read on through this paragraph, the next sentence says:

"In contrast, there are no concerns regarding the long-term side effects of newer ASMs used in first and second-line treatment."

Now, we have seen -- and I think you have explained this at least in part -- that your study from 2013 considered that lamotrigine and levetiracetam were associated with long-term side effects. That is right, is it not?

A. Yes. But I think that I already made the point, I do not think that I would consider them chronic, they might be not exactly chronic, and levetiracetam, lamotrigine and lacosamide, lacosamide has been around since 2008, lamotrigine was launched in 1991, levetiracetam was launched in 2000. We were using these drugs much earlier, for instance, I have been using levetiracetam

since 1994, I was using lamotrigine since 1986, and we were using lacosamide at least in 2004.

So you could argue that this is all well over, well, ten years, and with the way that we do it, I am not saying we are not going to pick them up, but they are going to be rare because the exposure to people already been quite large, and people are taking them, you know, you could argue for over twenty years.

Q. Just to be clear, Professor Sander, I think I am putting a more sort of simple point, which is that your study in 2013 considered that lamotrigine and levetiracetam were both associated with long-term adverse effects?

A. That is, yes.

Q. So that is not what you say here in the second sentence of your expert position paper.

A. I already clarified that. I mean different things. I think it is fair to say that things have moved on since 2013, and probably we would have put them on a different way then from now.

Q. Okay, so this is a reflection of your views now, not your views during the relevant period 2012 to 2016?

A. That is definitely the case here.

Q. Professor Sander, can I take you briefly to {XE4/6/3}.

In fairness, I may have asked you an unhelpful question earlier for which I apologise, but if we look

at -- these are your instructions from the CMA, and if we look at 2(d) you were asked to assist the CMA in relation to:

"Phenytoin sodium's role as an AED for new patients between 24th September 2012 to 7th December 2016 ... including where its use sits amongst other third-line AEDs and the main reasons for this."

So it is fair to say that that is what the CMA has asked you to do --

A. Yes.

Q. -- but it is also fair to say, is it not, that your position paper and to some extent your expert report actually has, if I can put it this way, inevitably, perhaps, because of the state of your knowledge, has dragged the timeline a bit, is that fair?

A. Yes, I think it is also fair to say that I am on the record being not very happy with the use of enzyme inducers back in 2012. So I think that that has not changed. If anything, it has become stronger during the period. So I am very clear that as back as 2012 I was already telling and I have slides showing you know the problems associated with enzyme inducers.

Q. We are going to come back to enzyme inducers just so you are reassured in that respect. Can we go back to

paragraph 36 on {XE6/9/9}.

The final sentence here:

"Some cosmetic side effects, such as gum swelling, hirsutism ... severe acne and roughness of facial features, are almost unique to phenytoin."

Can we go back to your study from 2013 at {F4/11/5}. If we could zoom in at the top under "Skin and cosmetic". So here we have absolutely clearly, gum hypertrophy is uniquely associated with phenytoin, but alopaecia, hair loss/thinning, associated with four other drugs, not phenytoin. One of the things you mentioned in that paragraph as almost unique to phenytoin, hirsutism, primarily or largely associated with valproate, also phenobarbital, phenytoin and I confess I have forgotten what PRM is, acne, again, something you have said was almost uniquely associated with phenytoin, largely here associated with valproate, phenytoin secondary.

So again, is this an example of your opinion changing between 2013 and now, or would you moderate the final sentence of paragraph 36 to bring it into line with your study from 2013?

A. I think that it reflects more what I think now. I have seen definitely very bad cases of acne amongst people with -- taking phenytoin. I have seen the least one

person on lamotrigine that developed acne, but I think that if you want me to say this is something that has moved on from where we were in 2012, but already was flagged up as a problem then.

Q. So it is flagged up as a problem, but it is not fair to say that these things are almost uniquely associated with phenytoin, at least as of 2013?

A. If you were to put it in numbers, if you, let us say, how many of these would be happening, probably we would have the picture, but I accept that they are not entirely unique.

Q. No, but just to come back to the numbers, valproate is in bold for the hirsutism and acne, two things that you said in your position paper were almost unique to phenytoin and the fact they are in bold here means that greater numbers of patients suffer these side effects as a consequence of valproate than phenytoin. That is right, is it not?

A. That is correct, yes.

Q. Thank you. Can I ask you just briefly about cardiovascular side effects. Professor Walker's evidence today was in 2012 what we knew was that phenytoin was associated with elevated cholesterol, patients were given statins, but that whether or not there was a connection between adverse cardiovascular

outcomes and phenytoin was, as he put it, anecdotal at that point. Is that a fair summary of the state of the science at that point?

A. I think that that would be correct, but I am -- one of the reasons I stopped using enzyme inducers in the way I did was because of my perception of the association of problems because one of my major research interests, as I pointed out, is mortality, premature mortality and co-morbidity. So I have written quite extensively about that before, before the period. So at that time in 2012 I already -- and you could say anecdotal, but I had that and I have not changed my mind, if anything it has strengthened my views that this is a problem with enzyme inducers.

Q. Just very briefly in terms of sexual function and sex hormones, that is not a side effect that is unique to phenytoin, is it?

A. Probably not.

Q. Can we move on to talk briefly about enzyme induction in AEDs and can we have {XE4/6} and page {XE4/6/7}. If we look at (d), if we could go down the page -- that is a bad reference, my apologies.

Let me put this to you and see if you agree with it. My apologies, the mistake is mine, but in your report you had described enzyme-inducing AEDs as drugs of last

resort. That is right, is it not?
A. That is my personal view, if you want to consider this, I would not want to use an enzyme inducer.
Q. Carbamazepine is an enzyme-inducing AED, is it not?
A. Correct.
Q. And that was the first drug recommended by NICE in 2012 for focal epilepsy. That is correct, is it not?
A. Yes, it was one of -- yes.
Q. You were using carbamazepine in 2012, I presume?
A. I was using it more than phenytoin, but my stop using it started around that time, it may be a little bit earlier.
Q. So you stopped using it at around the same time that NICE recommended it as the first-line drug off the rack?
A. That is probably correct, yes. I was always unhappy about carbamazepine being where it was.
Q. Oxcarbazepine is also an enzyme inducer, is it not?
A. That is not strictly correct. You have to go to very high doses. Enzyme induction starts at about 1,600, 1,800.
Q. Right.
A. So if you leave the dose under that, you do not have this problem, but I put my hand up, oxcarbazepine has more hyponatremia which is another bee in my bonnet, because particularly as people become senior, so it is

not any more flavour of the month as it used to be because it was carbamazepine without the full induction.

Q. I am grateful, and valproate, as we have already discussed is an enzyme inhibiter, so it is not the same thing but it has an effect on the same pathways within the liver; that is right, is it not?

A. Yes.

Q. That was a first-line treatment recommended by NICE in 2012?

A. Yes. I think that it is very important here that valproate should not be put on the same -- valproate is quite unique. Whilst for phenytoin we have many options, for a number of people with focal epilepsy this is the only drug that works, and for many people that is the difference between, you know, death and SUDEP, for instance. We do not have this in focal epilepsy, but in generalised epilepsy this is a problem. It is not a drug that I would like to -- I like. I do not think it is really a nice drug. It has loads of problems. However, we need to recognise its uniqueness, and if -- I would like to see something coming through would be a drug to replace valproate without the problems associated not only on teratogenicity, but other problems.

Q. So did you avoid valproate from 2012 onwards, or were

you prescribing it?

A. No, I would not avoid it, because I know for people with generalised epilepsy that would be the drug. I would try something else first, particularly in females, but it was my first-line drug for males at that time. I think that we had a situation which is well known, I have extensively written about this, this was an epidemic of death in Scandinavia when people got concerns about valproate and females, and there was a recommendation that people should come off -- girls should come off valproate and put on another alternative drug, and there was a series of deaths, and this then was blamed on the drug that they were switched to, and for a while there was a concern that lamotrigine was actually triggering sudden death, but after this was fully investigated and looked, it was clearly that it was because this drug was not working for these persons, they had a convulsion and they died as a result of that.

So I think that we need to make this disclaimer, and I am -- I would love before I go that we have a replacement, but at the moment we do not have that.

Q. That is very helpful, Professor Sander. The reason I took you to the wrong -- just to round out the picture, I said go to (d) on the page that is on the screen, but it was the (d) at the top, not the (d) at

the bottom, and that is what has thrown me. That is where you say:

"Therefore [enzyme-inducing] ASMs are now the last resort treatment alternative for people with epilepsy..."

Professor Sander, is it not something of an exaggeration to describe enzyme inducers as drugs of last resort when NICE put them first-line as drugs of first resort in 2012, so we are talking about carbamazepine here: NICE says it is the drug of first resort.

A. It was NICE that said it, they had their reasons, but it is not a drug that I would have put as a first line at that time, because of its enzyme inducing. This is, as I said -- and I would repeat -- this has been a longstanding issue I have.

Q. Yes, you have been very clear about that, thank you. Could --

A. And please do not take it that it is phenytoin. Here I am talking about enzyme inducers, particularly strong ones.

Q. Yes, well, you have described it as a bee in your bonnet. That is fair, is that right, and a long-term one?

A. Correct.

Q. That is helpful. Could we move on to talk a bit about how drugs become first, second or third-line treatments, and your evidence in your statement -- and I will not turn it up because I think it is not contentious -- is that whether a drug is first, second or third line is a question that concerns really the package of the drug as a whole, and I think we are agreed on that, but what I would like to clarify as regards phenytoin is what is in the package.

We have agreed earlier, have we not, that the best evidence from the Cochrane study was that phenytoin was as or more effective than carbamazepine, lamotrigine and valproate, the first-line drugs?

A. Yes.

Q. That is right, is it not? So its position in the third line is nothing to do with its effectiveness, is it?

A. I think that you -- we need to sort of make sure that I am not speaking for NICE and a decision that was made in 2012, so I cannot actually say why that happened then.

Q. Okay, well, let us carry on, if we can, and if you feel like you cannot give evidence as to why NICE has placed a drug in a third line then we can close down this line of questioning, but you have also agreed, regarding the package, that the acute and the idiosyncratic side

effects of phenytoin are similar to other drugs in the first and second line?

A. I agree, yes.

Q. As regards the chronic side effects, you have agreed as regards number they are similar to drugs in the first line, and as regards seriousness, you have also agreed that those other first-line drugs give rise to very serious side effects in equal number?

A. That is not exactly what I agreed. I agreed that they were probably of different severity, and this is what I still think and that was my view for a long time.

Q. I will not tread over that ground again, but is not the key point to take away from all of this the reason that phenytoin was a third-line treatment in 2012 was the relative difficulties of using it, the narrow therapeutic index and the non-linear pharmacokinetics. That, when we look at the package, those are the reasons that phenytoin is third line, because in other respects it is comparable to the drugs that are first off the rack.

A. You know, that is what -- you know, I am happy to go along with that.

Q. I am grateful.

THE PRESIDENT: Well, let us be clear, are you happy to go along with that because you do not know anything to

contradict it, or are you agreeing with the point that is being put?

A. No, I am saying that I was not part of the decision of why this was done at the time. That is what I am trying to say.

THE PRESIDENT: I see, thank you.

MR JOHNSTON: That is very helpful, thank you.

Could we turn to {XE4/6} and to page {XE4/6/8} and to (k) right at the bottom. In fact we may need to go over the:

"It is a fact that hardly any person with newly diagnosed epilepsy is started on phenytoin ... and this was already the case during the ... period 2012-2016. This is reflected in national guidelines, such as those produced [with] NICE ... which considers phenytoin a third-line option or a last-resort drug ..."

So what you are saying there when you use the words "last resort drug", at least here you are saying last resort drug means third-line option, the two meaning the same thing?

A. Correct, because there is no fourth-line.

Q. At this point you are relying on the NICE guidance to inform that conclusion?

A. I do not rely. You know, guidelines are guidelines. They are there to, you know, give you some ideas of how

things should be done. They are not written in stone, and they may change, as they did. So I think that guidelines need to be taken not as, as I said, with a pinch of salt.

Q. That is very helpful. Could we go to page {XE4/6/10} within this document and paragraph 18, three-quarters of the way down.

Here we have again:

"This is the third-line drug, or as often known, the drug of last resort ..."

That is sort of two-thirds/three-quarters of the way down.

"... as suggested by NICE and other guidelines."

So what you are saying when you use this term "drug of last resort" again here at least is that it means the same thing as third-line treatment?

A. It means the same as third-line because there is no fourth line.

Q. Understood.

A. But that is the last option.

Q. I am just trying to clear the semantic minefield if I can.

A. I am very happy to say that as NICE suggested, it was a third line, but the drug of last resort is something that I use and other people use.

Q. But not NICE?
A. No, NICE did not use that, no.
Q. That is helpful. So if we could go now to page {XE4/6/13} and paragraph 49. Sorry, actually we are now going to the position paper, so that is {XE6/9/13}, paragraph 49, because here you go a bit further and you describe phenytoin:

"Within the tail-end cohort of third-line treatment options for epilepsy, my view is that phenytoin is likely to be the worst option for most."

So you are not just saying it is third-line, therefore drug of last resort, you are saying worst option for most.

A. Yes.
Q. But as we have just agreed, there is nothing within the NICE guidelines that supports that conclusion. They do not say: third-line treatment, phenytoin is the worst for most. They say: here is a list of potential third-line treatments?
A. That is correct, this is my view.
Q. So you are expressing your personal opinion?
A. Yes.
THE PRESIDENT: And that is based on phenytoin's implication as an enzyme inducer, is that the main reason or are there others?

A. That is one of the reasons, yes, a strong reason.
THE PRESIDENT: What are the others?
A. I think the fact that the non-linear kinetics, the enzyme inducing, the chronic side effects. I have never disputed that it does work for some people, so it is the package, as I said earlier.
MR JOHNSTON: Yes, that is very clear, thank you.
You put it slightly higher again at the end of your position paper. If we could go to page {XE6/9/15} and paragraph 60, you say:
"In summary, phenytoin is rarely prescribed for very appropriate reasons; when prescribed, it will rarely lead to seizure-freedom."
Then you say:
"It has no place in my practice."
In fact, you have said earlier that you do not think you have prescribed it for 10 or maybe 20 years.
Just to tease this out a bit, it does have a place within the NICE guidelines, does it not, in 2012 --
A. Yes.
Q. -- and in 2022, but your evidence is that you do not even consider, is that right, treatment with phenytoin?
A. That is correct, I avoid it if I can. Having said that, I have started someone, as I said, recently, so because there was no other option this person had tried

everything, and so it is not that -- it has no place in my practice, but, you know, there is always exceptions.

Q. Okay, so we need to qualify this, do we, and say: it has some place in my practice, albeit rare; is that a fair summary?

A. Yes, very rare. I do not like to using "very", but let us put "very" in and then I will accept the "very".

Q. Okay, that is helpful clarification, thank you.

Could we go to page 15 in this position paper and paragraph 35. That is a flawed reference. I am looking for the phrase:

"I don't think any neurologist would recommend phenytoin..."

Mr O'Donoghue is rarely anyone's assistant but...

A. I cannot see anything.

Q. Yes, it is not in paragraph -- do you know what, Professor Sander, this is my mistake. It is in your witness statement. This is my mistake of moving between the witness statement and the position paper. It is {XE4/6/15}, paragraph 35, near the end, that is it, second to last sentence:

"I don't think any neurologist would recommend phenytoin to be used by their family or friends."

So just so I am clear, that is your evidence that no neurologist would recommend phenytoin to their family

and friends?

A. I do not -- I say "I don't think any neurologist would recommend phenytoin to be used by their family or friends", and I think that that should be the case.

Q. No, there is a difference between what should be the case and what is the case --

A. Yes.

Q. -- and we do need to be careful about, this Professor Sander. Your evidence is that you do not think any neurologist would recommend phenytoin to be used by their family and friends.

A. I am entitled to a view.

Q. But is this not a question of fact, not a question of opinion? Let me test this another way. So Professor Walker has given evidence that he does prescribe phenytoin --

A. Yes.

Q. -- to some new patients and we have also heard evidence that he has had referrals from neurologists, other neurologists who prescribed it; that is right, is it not?

A. Yes.

Q. We also heard that he has spoken to people within his department and a number of them have said that they prescribe it?

A. Well, the department that Professor Walker works is the same as I work.
Q. Yes.
A. And as I said this morning, we had eleven prescriptions in 2022 by three neurologists which means that 16 did not prescribe it.
Q. We will take it there, then. So even in the last year, leaving aside 2012 to 2016, on your evidence three neurologists in your department have prescribed phenytoin?
A. Including me.
Q. It is right, is it not, that neurologists contribute to the NICE guidelines and contributed to the 2012 and the 2022 NICE guidelines?
A. Yes.
Q. In fact, in 2022 -- and you may not be aware of this and if you are not then do not feel the need to answer the question -- it was actually the neurologists contributing to the guidelines who lobbied for phenytoin's inclusion, and --
A. Well, I think that if you were to ask me, I do not want to see -- I think that any drug that we have, you know, I am not saying it should be banned, that is not what I am saying, but, you know, it should not be -- it should be a drug of last resort, that is my view, it is

clear, and I would definitely think that phenytoin to be used by the family and friends is how it should be, it should be the last resort, and the last resort is that the exceptions that confirm the rule.

Q. But Professor Sander, I am going to have to test this a bit because you said here you do not think any neurologist would recommend it to family and friends, but I think we are clear, are we not, that the evidence is that neurologists, at least some neurologists, do prescribe it to their patients, and that is not because they are treating them worse than their family and friends, is it?

A. That is -- well, that could be correct, but I am entitled to my views here.

Q. No, no, I agree, it is just a question of fact, not a question of opinion.

A. Yes.

Q. So NICE definitely does not agree with that view, does it?

A. Yes, I agree with that.

Q. Because NICE's view is that it is recommended for friends, family and foes alike. Okay, can I take you to paragraph 52 of your position paper, please, so that is {XE6/9/14}.

You describe phenytoin here as -- here we go:

"Professor Walker states that phenytoin remains a helpful drug, citing three use cases: in an emergency setting ... as a first-line treatment ... and [also] as an add-on ... In Sander 1, I disagreed that phenytoin remains relevant and valuable ..."

So it is your evidence that phenytoin is not relevant and is not valuable?

A. Well, it is how you define relevant and how you describe valuable. With less than 3% of the prescriptions being for this drug and we already established that the most patients are legacy patients, I do not think that this is really a relevant drug. You know, where do you start with the relevant? 1%? 5%? So I would -- I still think that it is not such a relevant drug these days.

Q. Okay, can I qualify this, then? You are not saying -- you say you disagree that phenytoin remains relevant and valuable here, but actually what you are saying is it has at least some relevance, and by implication at least some value. That is your evidence is it, today?

A. If you ask me, I think it is not a relevant and valuable drug, that is my view.

Q. But phenytoin is relevant and is valuable to patients who are stabilised, is it not?

A. That is correct, I do not dispute that, yes, and I have a number of legacy patients and for them this is -- what

I am saying is moving forward, as a new drug or as a starting drug, it is not relevant anymore.

Q. Okay, so there is a distinction: it is relevant and it is valuable for patients stabilised on it?

A. For the people taking it, yes, and I do not dispute that.

Q. And it is relevant and it is valuable to the smaller cohort of people who try it for the first time if it works, is it not?

A. I still -- I am still waiting to see someone that this will apply. We now have a new drug, and Professor Walker mentioned it this morning called cenobamate, and we are getting in this cohort of people that we would be -- that have tried everything, including phenytoin, we are getting people seizure-free at rates around 30% at least.

Q. Can I just take you back to phenytoin for a moment and that is very helpful contextual background, but it is relevant and valuable to a patient who, even if you do not prescribe phenytoin, we understand that others do, who cannot be stabilised on another drug when phenytoin works for them, it is relevant, and it is valuable, is it not?

A. For people that are taking the drug, if it has worked and they are stable and they do not have side effects

for that person, it is, you know, I have no issues in saying it is relevant for that person.

Q. The NICE guidelines in 2012 did not say phenytoin is not relevant and it is not valuable, they said it is relevant and it is valuable for new patients -- not those stabilised on it -- for new patients as a third-line treatment, did they not?

A. That was their right, they can say whatever they want.

Q. Can I suggest to you that your conclusion that phenytoin is irrelevant and it has no value is something of an outlier within your professional field?

A. I would not agree with that. I think the question is we need to ask colleagues, and I know many colleagues in many countries where this drug is not used anymore, and even when we are -- this drug is a WHO essential list drug, but we go to countries where I do a lot of work and people do not want phenytoin because of the perceived problems of the drug. So I think that -- and as I said, nowadays with the changes in the demography, and I accept that this was not the case in 2012 as strong as it is now, this drug now has become, you know, for people going forward, I do not think it is a relevant drug anymore.

Q. That is very helpful and that may be a part of the answer, which is that in 2012 to 2016, the position that

you have set out in your position papers and your expert reports, it would have been an outlier then but what you are saying is it is potentially less of an outlying position now?

A. That is probably correct, yes. I think that my practice has been making sure that the patients get the best deal, the best drug, and we do not have to mitigate or manage; we need to prevent. And I think that that is a very important part of what I see the practice of medicine: do no harm.

Q. Yes.

A. So this is why I do not like drugs that are enzyme inducing, drugs that cause hyponatremia, because you know, once you take people off a drug that causes hyponatremia, people will come back and say: my life is different, my life is better. I hear that so many times of people coming off phenytoin: I am feeling much more alert, I am feeling much better since you switched me to this other drug, thank you for taking so long to convince me, I should have been convinced at the beginning.

Having said that, probably a similar number of people did not want to change, carry on, and, you know, I am quite happy for this, if people know if that is their decision.

MR JOHNSTON: Professor Sander, that is very helpful.

Sir, I have no further questions. I am mindful of the time. I have not left you a lot of time for questions and I know you will have at least some, but I am very grateful.

THE PRESIDENT: Not at all. Thank you very much, Mr Johnston.

Questions by THE TRIBUNAL

THE PRESIDENT: Professor, I think you were in court when I went through various scenarios with Professor Walker, so you will know roughly the thrust of my questions, so I will try and take them a little more quickly, but if you want me to slow down, do say, and I obviously want your fullest answers, not just yes's and no's.

So let us start with a new patient who is diagnosed an epileptic but who has yet to be subjected to a regimen of drugs, and to be clear, we are talking about the period 2012 to 2016, so if you could go back in time, I appreciate it is difficult, but try if you can.

Now, we know that even in that time, the first and second-line treatment of drugs would not include phenytoin.

A. No.

THE PRESIDENT: So if you have a situation where the issue

of seizures is resolved using first and/or second-line drugs, we do not get to phenytoin at all?

A. That is correct, yes.

THE PRESIDENT: And you are very happy about that?

A. Yes.

THE PRESIDENT: So we are talking about the case where there is a seizure occurring notwithstanding the deployment of first and/or second-line drugs.

Now, in those circumstances, you have to balance the desire to avoid a seizure against the side effects of any drug that might prevent that, and that is a specific question you will ask at every stage, but I am asking it at the third-line of creating a drug regimen.

Now, in those circumstances, I quite understand that your view as to the running order of third-line drugs will have phenytoin in last position. Would that be fair?

A. I think it is fair to say that I would not -- for the reasons Professor Walker mentioned this morning, I would not be using vigabatrin because a third of the people will develop visual problems. I think that that is a far too high risk, and I feel guilty for not having picked up this two years before it was reported when a patient of mine who was a farmer came to me to complain that: after 35 years milking cows I never was

hit by a cow, now since you put me on this drug I have been hit by the cows, they probably do not like the smell of the drug, but this patient was developing visual field defects, was getting blind and he was walking into the cows, and I felt guilty for a long time I did not pick this up. So I have not used this drug for probably well over five years.

If I need to use a drug from that group and if the person has not been exposed to phenobarbital, I will use phenobarbital ahead of phenytoin. Tiagabine, which is the other drug mentioned, the only surprise with this drug is when it works, so I do not try it, I do not use it, I have given up on that.

So my order of third-line drugs would be phenobarbital would be the drug of last resort. But to get there, it will take many, many years --

THE PRESIDENT: Sorry, drug of last resort meaning it is at the end of the list or the beginning of the list?

A. A third-line drug, sorry, the third-line drug.

THE PRESIDENT: Right. But the only third-line drug you would use?

A. Well, you know, that would be the one that I would try first.

THE PRESIDENT: Well, that is my question, Professor. I mean, look, we are all agreed that this is

a patient-subjective question, so you will be looking at the patient in question, and it is going to be a somewhat nuanced question because that patient will already have been subjected to a regimen of one and maybe two drugs, the first and second-line drugs, in order to control the problem.

A. They probably would have been exposed to many more drugs.

THE PRESIDENT: That may well be the case, so it is a complex situation, I understand that.

A. Yes.

THE PRESIDENT: What I am seeking to understand is the circumstances in which you would deploy a third-line drug and in what circumstances within that range you would deploy phenytoin as that third-line drug, and let me capture what I think you are saying.

What you seem to have said -- and do correct me if I am wrong -- is that you would not do so save in the most extreme of circumstances, because you said: I avoid it if I can and it has no place in my practice.

A. That is correct, but no place in my practice there is always exceptions.

THE PRESIDENT: Yes.

A. The rule would be I would not use it, but having said that, if there is a situation, my job is to get the

patient seizure-free without side effects, but we only should, you know, cross the bridge of the last resort, third-line, if we have tried everything else. The person coming with the first seizure to the time that they will come to the situation of a third-line drug will be years. What happens is often we get referrals both, you know, as a service, of a neurologist that send us saying: this patient has tried this or has tried that, is there a place for surgery or other treatments. In my experience, most often than not there is a lot of therapeutic nihilism outside the sort of epilepsy community, the epilepsy neurologist, because people have not tried many of the drugs that are available.

So, you know, even when I get a tertiary referral, I will be using drugs that should have been, like, for instance, lacosamide or perampanel, nowadays we have cenobamate, and I have this problem of therapeutic nihilism is really something that is another bee in my bonnet, because the drugs are out there, people are suffering seizures and they have never been tried because people, for the reasons that Professor Walker articulated this morning, do not think that 5% better seizure-freedom is a good, you know, outcome, so I do not do anything.

So the default in a lot of places is no changes:

people stay on the same drug, this is the best we can do. The other problem is that a lot of neurologists they have in their mind what I call the regulatory outcome, and this is that the regulatory outcome is usually a 50% seizure reduction. That is fine for the FDA, that is fine for the [MHRA] but for patients, a 50% seizure reduction is no good, it does not change quality of life, and as one patient told me once: you are asking me to, you know, consider a 50% seizure reduction, it is like asking me to jump from the fifth floor instead of the tenth floor of the building. I think that this was very -- that resonated on me. The only thing that will make a difference for a patient is they become seizure-free and my job is to give them the best chance to become seizure-free.

However, there are people out there that do not want that because they feel that their benefit might be put on place, they may feel that: if I stop having seizures I cannot go anymore to the epilepsy support group, so there is a lot of reasons, and we need to take every individual opportunity, you know, of these issues until we come to the drug.

If a patient comes to me saying: I have read, Dr Google told me that the best drug for me will be this one, I will discuss, I might not agree, I will try that,

and it is not a case of phenytoin, but at least twice it happened that people came with preconceived ideas which drugs they could have, and of course that they were convinced because Dr Google told them, and even against my best professional judgment I could not convince them, so we started them on the drugs they wanted, and, you know, I do not know the outcome in one of them and the other one it did not work, but he already had a second opinion, from probably Dr Yahoo! on which drug he should try next, but, you know, if that is what people want, I will go along, so it is very important that we take decisions.

The other thing is that the reason people have breakthrough seizures, we need to find out: people do not take the tablets. They had fever, they had something that happened.

THE PRESIDENT: Well, pausing there, we will be coming on to the patient who is on a regimen and the change in a moment. We are here talking about the patient who has just been diagnosed with epilepsy and we are working out a form of treatment.

Now, just to understand your disinclination in relation to phenytoin, is it this: you accept, I think, that phenytoin is effective as a third-line drug to combat and ideally eliminate seizures?

A. Correct. I said that, that it is effective for seizures.

THE PRESIDENT: I am just articulating my understanding so you can correct me. So the reason you do not want to put a patient, a new patient, on a regimen that includes phenytoin is because your perception of the side effects is that they are so deleterious that one ought to try other drugs in preference to eliminate the seizures?

A. That is correct, yes.

THE PRESIDENT: So what you will be doing is you will be explaining to your patients the risks and rewards of a certain course, and what you will be saying -- and do correct me if I am putting words into your mouth that do not belong there -- what you will be saying is: well, phenytoin does have an effect in preventing or reducing seizures, but you should know that it has a number of side effects regarding enzymes and enzyme inducement that mean that we ought to explore other third-line drugs before that?

A. That is correct, and I think that I tend to draw whatever sort of the pros and cons of each drug, and there is always the -- I do not have any doubts that efficacy is there, particularly if we were to use it earlier, but, you know, once we get to the side effect and other problems, my problem is the enzyme induction.

I think that in a few years' time when -- I have already seen the case in the United States, there is litigation for people that have pathological fractures as a result of enzyme inducers. I have seen one case of someone with carbamazepine with this problem in this country. So we are going to start seeing this, and there is a number of studies looking, and nowadays with data-mining it will not be long before we will find out the impact of enzyme inducers in someone's life.

So that is why I have this problem.

THE PRESIDENT: No, no, it is not a problem; it is your view.

A. Yes.

THE PRESIDENT: And you have said on a number of occasions that you are entitled to a view, and let me be clear, I entirely accept that, but let me spin the question round, and again we are still talking about the new patient. If you have a different physician, let us say Professor Walker, and you hear that they have explained the side effects of phenytoin differently to you, with less emphasis, and have deployed phenytoin higher up the running order of third-line drugs, would you accept that they too are entitled to their view that that is a legitimate form of clinical judgment that they can exercise?

A. Yes, I think that is part of their clinical judgment.

THE PRESIDENT: I am grateful. So moving on to the next stage, we have a patient who has been on a regime of phenytoin, so there is a stickiness, if I can use that term as I did with Professor Walker, to the demand for phenytoin to that patient, and I hypothesised three different cases which might come to a doctor, and let me just summarise them and maybe we can take this a little more quickly.

The first was an instance where a patient two years free of seizures has suddenly had a seizure and, therefore, is no longer stable, and in those circumstances they would end up before a consultant either directly or indirectly via GP referral.

The second case is where there is stability, there is no seizure, but there is a perception on the part of the patient that there were increasing side effects which concerned that patient and there we have the GP acting as a preliminary filter, and if the GP considers that there is a causality between the side effects and the regimen of treatment, again, it will be escalated to a consultant to take a view.

Then the third case was where there was no concern on the patient's part at all, so no seizure and no perceived concern regarding the side effects, and there,

1 although the patient would be regularly coming before
2 their GP for blood tests and repeat prescriptions,
3 nothing would happen, that was at least
4 Professor Walker's evidence.
5 Now, broadly speaking, do you agree with those
6 categorisations?
7 A. Yes, I think it is fair.
8 I think that that is quite a fair -- if someone has
9 no problem, seizure-free and there are no concerns from
10 blood tests, and after a certain age I think it is
11 important as well to do bone density scans, you know,
12 then so be it. Because the risk of someone having
13 a seizure coming off -- the first question would be this
14 person needs their medication, but, you know, we know
15 that the risk of coming off medication is quite high in
16 terms of seizures. So if they do not need a seizure,
17 would it be better if they come off the treatment, or if
18 they have concerns should we try something else, but at
19 the end of the day, you need to be very clear with the
20 person all what it involves, because having a seizure as
21 a result of iatrogenicity, and I learned a big lesson
22 when I was just a recently-appointed neurologist. At
23 that time, I convinced a gentleman who was my patient to
24 come off drugs, he had been referred by the GP because
25 he had gone over twenty years without seeing

a neurologist, and this person was taking a relatively high dose of phenobarbital, and I said this is really -- and I said, you know, this drug really causes problems to your cognition, this is no good, we should consider you coming off, and I remember this well, and I tell you why, he told me: but I am very, very well, I am the finance -- CFO of a big corporation. I said: well, you know, if you had been off this drug that probably is causing problems to your cognition, you might have been the Prime Minister, you might have been the CEO of a major company, and I convinced him to come off this drug.

Eleven days after the last dose of this drug, this man was found in a hotel, had died of SUDEP, and that is when the half-life of -- well, when phenobarbital has fallen under a certain -- and that was the first time I lost a patient, and that was a real shock, and his wife who was against him coming off drugs, mainly because she had to drive, called me a murderer, and this for me was a really big lesson in terms of how I should behave as a person and why I should have listened. I tried to really convince him quite hard. I would not do this nowadays. So it is very important that we explain everything that could happen, and the risk of SUDEP, the risk of -- if we restart seizures, it is not

always easy to stop the seizures again, even if we replace the drug. That is like the seizures are kindle -- rekindled when you come off drugs, and then you have problems in stopping them.

So all these things need to be expressed to the patients and I often will write a letter saying what was our discussion, I tell them to go away and think about it, and I have a gentleman who I am trying to convince for the last two years for him to come off an enzyme inducer which is not phenytoin but carbamazepine, and I have not been quiet -- because he has concerns of seizures coming back. Then recently, after 29 years seizure-free, he had one seizure, he had to stop driving and everything. Now he is very engaged in changing. So you need to treat each situation on individual merits. You need to find out if there was any trigger for a breakthrough seizure, and the commonest is people not taking the tablets. The problem is often people forgot about it or they think that a doctor will tell them off because doctors are known to be authoritarians, so they will not tell the doctor, and your tendency will be let us change it because -- but if you know or identify that not taking the drug was the trigger for the seizure I would be very happy to leave them without any changes provided that they stick to the -- you know, to adhere

to the treatment.

THE PRESIDENT: Professor, that was very helpful. Can I put this to you, and you can then tell me whether it is a fair summary. You heard, again, what Professor Walker said this morning in response to this type of question. Can I suggest to you that actually your response to patients who are on a phenytoin regime coming before a consultant like yourself or like Professor Walker, your reaction would not be very different to that described by Professor Walker when he gave evidence?

A. Would be no different.

THE PRESIDENT: Except, perhaps, this: you might say a little more about the enzyme inducer risk than he would?

A. Yes.

THE PRESIDENT: You might be a little bit more emphatic?

A. I do not know what he says, but I definitely would go on about it.

THE PRESIDENT: I am sure would you go on appropriately, Professor.

Thank you very much. I think you might have some questions from Professor Waterson.

PROFESSOR WATERSON: Just one question, I think, and I should perhaps have asked this earlier to Professor Walker, but we have heard about the words

"high dose" and "therapeutic range" in the case of phenytoin. Could you tell me what is the range?

A. That is how big is a piece of string. I think that it is fair to say that I have seen people, particularly slow metabolisers, that have responded to 75mg, but the average dose would be likely around 300.

PROFESSOR WATERSON: 200, sorry?

A. And give it 50 either way.

PROFESSOR WATERSON: Oh, 300.

A. Once we go over 300, we start to get very near for the -- where people would switch and then, you know, the side effects, but, you know, in my experience most of the time when people respond, have a good response to a drug, it is in relatively low doses. So with phenytoin, it is no different. So I would start someone on 200mg as we heard this morning. I will then maybe go up once I have the level, once people have the time to get to a steady level, and then I would go up by either 50 or 25 until the person is free of seizures. I think it is important that this is the only drug that I will use levels because of this issue.

Other drugs, my view is that I will only be doing levels if I want to check if they are taking their medication, which is different from in the case of phenytoin because of this non-linear kinetic.

PROFESSOR WATERSON: Thank you. That was all I wanted to ask.

THE PRESIDENT: Any questions arising out of that, Mr Johnston?

MR JOHNSTON: None at all, sir. I am mindful that we are at page 234, so the transcriber has probably broken a record for any hearing that I have been in, so I wanted to express my personal thanks to her, but no further questions from me, sir.

THE PRESIDENT: I am grateful.

Any re-examination?

MS MORRISON: Sir, I hate to be the annoying one at the very end of the day, but I just have one point that I wanted to pick up with Professor Sander.

THE PRESIDENT: Of course.

Re-examination by MS MORRISON

MS MORRISON: You were asked various questions about the NICE guidelines and you did say at one point you cannot speak for NICE, but you were asked:

"Question: The NICE guidelines in 2012 did not say phenytoin is not relevant and is not valuable, they said it is relevant and it is valuable for new patients -- not those stabilised on it -- for new patients as a third-line treatment, did they not?"

You were not actually at any point taken to the 2012

guidelines, so I just wanted to show you two paragraphs in those guidelines and just ask you after you have read those, I will show you them quickly, whether or not you disagree with anything NICE actually says in those guidelines.

So if we could bring up first {XD1/6/222}. Just to orient us, we are in the section where the 2012 guidelines, the public version, are discussing this and actually sir, it may make sense for the Tribunal to actually take a note of this, because it is very much worth, I think, you reading the following pages because it sets out the different ones.

We first have the first-line drugs, of which there are a number of other than some of the ones we discussed today. If we carry on down, we are going to 1.9.3.5 which is at page {XD1/6/224}, and I wonder if everyone could just read that paragraph. It starts:

"If adjunctive treatment ... is ineffective ..."

THE PRESIDENT: Yes, if you read that to yourself, Professor. (Pause)

MS MORRISON: Then if we could go forward to {XD1/6/779}, then there is the detailed underlay analysis that NICE did that underlay these guidelines, and at the bottom of the page is what underlies the recommendation that we have just read, and if we could just go on to page

{XD1/6/780} you will see on the left-hand side a column marked:

"Trade off between clinical benefits and harms."

Then the paragraph on the right-hand column starts with the discussion of phenytoin, if you could just read that paragraph. (Pause)

Professor Sander, you were asked the question about what the third-line guidelines meant, but is there anything in those guidelines that you disagree with?

A. Yes. It says phenobarbital is not recommended because of adverse effects, and I accept that, and that was a major -- let us put it that way, I used to have (inaudible) going out, but I think that I have slightly changed my view with this drug. We have done studies in Africa and in China and we showed that if you do not have to go over doses of 60mg, it causes very little problems, and it hardly ever affects the liver, but once you have to go over 90mg, the problems kick in, and you can clearly pick up cognition. So that is why I said earlier that I would use phenobarbital because I can get -- I know that we in this country tend to go -- when we use this here -- doses over 100mg, 150mg, but people that are naive to this drug, most of them respond to low doses.

So that would be my major disagreement with this.

Apart from that I think that clobazam is probably the most effective anti-epileptic medication, but 70%, 80%, of Caucasians developed tolerability.

Q. Just to focus in on phenytoin, is there anything in that discussion there that you disagree with in terms of the reasons given for phenytoin being a third-line drug?

A. No, no, I do not disagree.

THE PRESIDENT: Could we just go back to the first reference {XD1/6/224}. You were referred, Professor, to 1.9.3 5 and you see there what it says, and all I am going to ask is it references a series of other AEDs which include phenytoin. These are all third-line treatments.

A. Yes, and I think that of these drugs, lacosamide was relatively new then, eslicarbazepine is basically another formulation of oxcarbazepine, and if I wanted to use oxcarbazepine, I would be using oxcarbazepine. This is basically the non-racemic formulation of oxcarbazepine. It was initially sold by the drug company that this was oxcarbazepine without the hyponatraemia, but once it became public, once it was used in clinic, we saw that the effects on sodium levels was as much as oxcarbazepine, but it turned out that during the clinical development the drug company put a stop and anyone that had previously had hyponatremia to be included in the trial, so that was a fallacy. So

I would definitely think that lacosamide, phenobarbital and zonisamide would be drugs that I would consider and they have -- at least zonisamide has moved; tiagabine the only surprise when it works. So things have moved on from this, but I do not disagree with them.

THE PRESIDENT: Thank you. The point was going to make -- and do correct me because it is very much a layman's point -- was I was noting that the tertiary drugs listed were essentially, not completely, but essentially in alphabetical order, and I wondered if that reflected the fact that it is a matter of individual clinical judgment how one tries these in a given case, and that there is not being recommended a running order of preference. Would that be a fair characterisation of what we are getting from this paragraph?

A. I am quite impressed that you worked out they were in alphabetical order. I think that you are right. I have never thought about this, but, you know, there is no order in it. I do not think there is any ranking. It is probably just -- you know, these are the options that were available then. Two of these drugs have moved up in the food chain.

THE PRESIDENT: I am grateful.

Any questions out of that?

MS MORRISON: No, that is everything, sir, thank you.

THE PRESIDENT: Professor, thank you very much. I am sorry it has gone on for so long.

THE WITNESS: Thank you.

THE PRESIDENT: We, as with Professor Walker, enormously value your help, and we wish you well when you resume your clinics tomorrow. Thank you very much.

THE WITNESS: Thank you very much.

THE PRESIDENT: I am just checking the timetable for tomorrow, and I think we have another 10.00 start, is that right?

MS STRATFORD: Yes, that is my recollection.

THE PRESIDENT: That is absolutely fine. I just want to make sure we are all on the same page. Is there anything more we need to consider before we adjourn until tomorrow?

MS STRATFORD: Not that I am aware of, and obviously we are moving tomorrow now to the start of the block of economists accountant industry experts beginning --

THE PRESIDENT: We cannot wait, Ms Stratford. We are looking forward to it.

MS STRATFORD: We will be beginning with the teach-ins and swearing in each of the experts in turn before their respective teach-in is what counsel had understood would be happening.

THE PRESIDENT: No, that is very helpful.

I see that we have an appropriately generous amount of time for the hot-tubbing. Just to be clear that we found the teach-ins extremely helpful this morning. They both went on beyond their allotted time, and we were very happy for that to happen.

I anticipate that may be the case tomorrow, so we are going to exercise a light touch in terms of looking at the stop clock, but of course we hope that all of the experts will understand that time has to be taken from somewhere and the more time we have on teach-ins the less time we have for the hot-tub.

So can I urge everyone to be as concise as possible simply because we have a lot to learn and quite a lot to ask.

MS STRATFORD: Absolutely, sir. I am sure all of these experts will have prepared with the time limits in mind.

THE PRESIDENT: Thank you very much. Can I express my particular thanks to you for bearing with us. It really is appreciated. Thank you very much.

We will in that case adjourn until 10.00 tomorrow.

(5.09 pm)

(The hearing adjourned until 10.00 am on Wednesday, 15 November 2023)