IN THE COMPETITION APPEAL TRIBUNAL

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

Salisbury Square House
8 Salisbury Square
London EC4Y 8AP

Monday 6th November – Wednesday 13th 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

Thursday, 30 November 2023

(10.00 am)

Housekeeping

THE PRESIDENT: Ms Morrison, good morning.

MS MORRISON: Good morning, sir.

I just wanted to deal with a couple of corrections and an update on the question the Tribunal -- corrections and then a question that the Tribunal had for Mr Hawkins on some documents that might assist with understanding QALY first.

THE PRESIDENT: Yes, of course.

MS MORRISON: The first correction I wanted to make was there was a discussion yesterday about the rules that governed speaking to the experts during the course of teach-ins.

THE PRESIDENT: Yes.

MS MORRISON: Mr O'Donoghue took you to a part of the transcript from Day 5.

THE PRESIDENT: Yes, he did.

MS MORRISON: I just wanted to show the Tribunal {Day7LH1/5:4-11}. This was the first day of the hot-tub and when the teach-ins started, sir, and I think this might have been the passage that you were recalling where you, if I just read it out to everybody --

THE PRESIDENT: Well, that is the passage I was recalling,

and perhaps I could make clear what I am expecting from the legal teams in regard to how we deal with witnesses, because I did not find the altercations yesterday particularly helpful.

We have rules of purdah to preserve the integrity of evidence and to protect witnesses from, in effect, themselves. Those rules apply where cross-examination is taking place for obvious reasons.

The reason we have this passage and the reason the passage that Mr O'Donoghue took me to yesterday, which was much more attenuated, and I think ambiguous, is because teach-ins are different, and I hope that we will not have the kind of technical point being put as it was yesterday put again, and that is for two reasons.

First of all, we deprecate technical points and, secondly, it was clearly discombobulating to Mr Hawkins to be challenged in the way he was, so I will put down that marker, and we will proceed as we go next time, but I am sorry that you, the CMA, have been deprived of the opportunity of using Mr Hawkins to obtain the material that we requested.

MS MORRISON: That actually leads me on to the mea culpa I was going to come to later. We have not actually been able, overnight, without the assistance of Mr Hawkins, to find the right material. He actually referred to

some slides that he has ready-made on this, so what I was going to suggest is that later on we can then speak to him and we can get those slides and assist the Tribunal.

So really, I raised it because I have not been able to help in the way I would have liked to, sir, overnight, so I just wanted to raise that and correct --

THE PRESIDENT: Ms Morrison, that is absolutely fine. To be clear, I do not think there is any particular time pressure on this because we really just want to put flesh on the bones that Mr Hawkins was very helpfully articulating yesterday, and we will get the material as and when.

If, of course, it is such that other questions should have been asked but we cannot ask them because it is too late, then we will disregard the material and not use it, so that is how we will proceed.

MS MORRISON: Thank you, sir.

THE PRESIDENT: It is really just to get a flavour of how QALYs operate, and I am quite sure we will be further enlightened by the experts who we will be hearing from in due course.

MS MORRISON: I am sure Mr Hawkins will be able to speak to it more. He lives and breathes this in a way that no one else really does so I am sure he will be able to

assist.

There is just one other correction, I hear you completely, sir, on the technical points, we completely agree with that. I just wanted to also correct the impression that we had attempted to sneak something in or do anything. I just wanted to show you one email which explains why we had not mentioned the notes. If I could just hand these up to you. I am not going to take a big point, I just want to show the Tribunal that this is the basis we were proceeding on. (Handed).

THE PRESIDENT: Yes, of course. Let me read it.

MS MORRISON: This is an email from one of Ms Stratford's instructing solicitors. It is dated 9 November and it was about preparation for the hot-tub and teach-ins. There is only a single sentence I wanted to show the Tribunal. It is the very last sentence on the first page and it basically says:

"Our experts Raphaël De Coninck and Richard Williams are likely to use their own sets of notes to speak to during their respective teach-in sections."

So we were simply proceeding on the basis that it was not a memory test, and so we had no objection to anybody having any notes.

Now, I am not set a hare running, we are not interested in knowing whether any of my learned friend's

experts had notes for their teach-ins and we have no interest in seeing them for the teach-ins, their evidence is that which is said and what is in the slides. We have no interest in going behind it, but I just wanted to correct any impression that we were up to no good yesterday.

THE PRESIDENT: I do not think that was an impression that we at least had anyway, but I am very grateful for that.

I think I made clear yesterday that there would be no question whether you want to provide them or not, no question of us directing you to provide those notes.

MS MORRISON: We would have been happy to provide them, I just think it all became a bit discombobulating and I wanted to move us forward.

THE PRESIDENT: That is very helpful, and thank you for drawing this to our attention.

MS MORRISON: The only point I thought it was proper for me to flag this morning is we cannot do Monday, so I just wanted that to be very clear. There are issues for a number of relevant personnel.

THE PRESIDENT: I think Professor Waterson has also said we cannot do Monday.

MS MORRISON: Okay, well we cannot do Monday.

THE PRESIDENT: We cannot do Monday.

MS MORRISON: There we go. That is everything, so I am just

going to call Mr Hawkins for the rest of his teach-in.

THE PRESIDENT: Thank you very much. Much obliged.

MR JAMES HAWKINS (continued)

Teach-in by Mr Hawkins (continued)

THE PRESIDENT: Can we, while Mr Hawkins is taking his seat, pull up his slides because I am sure we will be going back to those and put them up on the screen. {XC3/1}.

Good morning, Mr Hawkins, welcome back. Do resume where you left off and we can take it from there.

MR HAWKINS: Sorry, I will get my bearings. I think we had finished with this slide, so can we move on to the next slide {XC3/1/15}.

We are now discussing how we calculate the ICERs and how do we decide if an intervention is cost effective compared to current practice which is the usual comparator in NICE economic evaluations. Essentially just your difference in costs on the top of the equation, so you would have two treatments, you would follow up the lifetime costs of one, the lifetime costs of the other and that is just the difference between them, and you would do exactly the same with quality adjusted life years, see how long they live for and to what standard of living those life years are, and it is simply just dividing your costs by your quality adjusted life years and that then gives you your cost per

additional QALY, and that is what we have been calling our incremental cost effectiveness ratio, and you can compare that to a threshold, what you are prepared to pay for your additional QALY, and in very, very simple terms, if it is less than that threshold, you would say it was cost effective, if it was more than that threshold you would say it was not cost effective. That is the absolute simplest terms you can describe that.

Next slide, please {XC3/1/16}.

So what is the threshold? At NICE, we always use threshold in inverted commas because NICE has never identified an ICER or a threshold above which interventions should not be recommended or below which they should, but we do have a guide threshold, a general principle that in technology appraisals anything which is less than £20,000 to £30,000 per additional QALY we would accept, often in technology appraisals which do go right up to the 30k threshold.

In guidelines, we tend just to use the lower of that range, £20,000 per additional QALY, but we do recommend technologies and interventions above those thresholds, we do reject interventions and treatments below that threshold, and just to talk a little bit about this threshold, I use it in inverted commas, it has been used since the inception of NICE in 1999, that value has not

changed since, we are almost 25 years later now.

There is actually a little bit of a dirty secret of NICE, there is very little empirical underlying that £20,000 threshold, and in fact, there is also an uncertain history about it. We do not actually know where it has come from. It just seems that one day somebody started using that £20,000 threshold. Nobody can trace it back, which seems to always shock people, but that is the truth.

THE PRESIDENT: One sees some references to 30,000; is that just my memory playing me false or --

A. So guidelines we use 20,000.

THE PRESIDENT: You use 20.

A. Technology appraisal we have the 20,000 to 30,000 threshold.

THE PRESIDENT: I see.

A. That is trying to catch the more innovative nature of technology appraisals, kind of an innovation premium within that threshold.

THE PRESIDENT: Thank you.

A. I talk about that in a little bit. But that 20,000 is meant to be a compromise between ensuring fair and equitable access, I am going to call that the opportunity -- sorry, my train was late this morning so I have been running so I am a little bit out of breath.

So that is a compromise between ensuring fair and equitable access to treatments, I am going to call that the opportunity cost part of the threshold: if you take money from one part of the NHS people are going to lose quality adjusted life years, so you would hope that you would gain that back wherever you put that money, and also about enabling access to new and innovative treatments which I am going to call the innovation premium part of the threshold.

If you read the literature, when people talk about what NICE should set their threshold at, there is an absolutely huge range with no consensus amongst economists. This is a little literature search that I did, very unsystematic, but I found ranges from 5k to 70k, saying that is what NICE should set their threshold at and in general, the 5k, the lower thresholds, they are pure opportunity cost. If you take 5k away from one place in the NHS you are going to lose one quality adjusted life year.

These higher values tend to be this opportunity cost and an innovation premium and I suppose depending on how much you value innovation, that is going to be that part of the threshold is going to be higher, but there is no consensus among economists of what it should be.

Just to say, as I say, we don't have thresholds, but

we do use other guide values at NICE, we have 50k for end of life care, that is treatments that add more than three months of life expectancy in the final two years of somebody's life, and then we have a threshold of £100,000 per additional QALY, and that is for highly specialised technologies, interventions and treatments, that is for very small populations of people, sometimes they are called orphan drugs, but, yes, so it is not 20k or 20k 30k for absolutely all interventions considered.

Next slide, please {XC3/1/17}.

So absolute value of a QALY. I know you have had some discussion previously in the Tribunal about this. So NICE cost effectiveness analysis is comparative, and it is usually compared to current practice. If that drug or that intervention did not exist, what would we do instead, and NICE does not have an absolute value of a QALY, we have never identified one, not even informally or formally.

There is no upper limit --

THE PRESIDENT: Just so that I have this clear, it is obviously very clear in your mind, Mr Hawkins, but what you are doing when you are looking at the cost benefit is you are looking at what you are already doing or what the practice already is. You are looking at the cost and the effectiveness in QALYs of that, and then you are

looking at the innovation or the new treatment or whatever it is that is new, and you are saying: applying the same QALY and cost effectiveness -- and cost questions, is this a better solution to the one that is already being used?

A. Yes, I would say that is what we are doing, because we are taking 20,000 away from somewhere else in the NHS to fund this potentially so you want to at least get your additional QALY, and that is the opportunity cost part of it, and there is some sort of innovation premium there that we are valuing newer treatments, innovative treatments.

THE PRESIDENT: But it is always an innovative treatment in contradistinction to or replacing an existing treatment, you are always comparing one form of treatment, the existing regime, with a new form?

A. It is sometimes older drugs, sometimes things that have been around for ages, but an alternative course of action, yes.

THE PRESIDENT: Yes, but what I mean is there are always -- when I said "old", I meant existing, not ancient. So what you are doing is it is like simultaneous equations, you have the existing process of treatment which is delivering a certain number of QALYs at a certain cost, you know those two, and then something new comes along

and you apply exactly the same metrics to that, and you say what does it cost, what is it likely to cost, what is it likely to deliver by way of QALYs and you compare the old, meaning the existing, with the new, meaning the not used but that you are assessing, and you are always comparing the two; is that right?

A. Yes, that is correct, it is always a comparator.

THE PRESIDENT: Okay, thank you.

A. A comparative analysis.

There is no -- well, there is no upper limit for resource impact from our recommendations. Once we start getting to the hundreds of millions, the billions, NHS England have something to say, but in terms of our methodology, there is no upper limit for resource impact, the overall cost of the recommendations. If something is cost effective and effective and there is strong evidence underpinning that, then we should recommend it regardless of the overall budget impact.

There is a little bit of a debate around whether NICE follow the principle of rule of rescue. I did have the exact definition in my notes, but NICE have a very, very narrow definition of rule of rescue which is a single identifiable person who needs life-saving treatment, and just to give NICE's position on these sort of things, there are many expensive treatments

available in the NHS and personal social services, so Libmeldy, which is in metachromatic leukodystrophy for children, that has a list price of 3 million although they are supplying it at a discount, I do not know what that discount is.

Round the clock care for complex needs, that is more than £200,000 per year. These are all an absolute -- if you look at them in absolute terms, I am not going to give you more -- there is going to be more than £20,000 per QALY.

On the flipside of that coin, there is also very inexpensive treatments. Aspirin can be life-saving if someone is having heart pain, so, yes, I mean, I have not been able to give you an answer on the absolute value of a QALY because NICE do not have an answer, I think it goes into the area of statistical life, and that is outside of the scope of NICE and it is outside of my own expertise, so I think the take away from this slide is that we do not have an absolute value of a QALY.

THE PRESIDENT: That is helpful. Just so that we are clear about what we are talking about here, this is a value that in some economies, I think the US do this, where you pluck out of the air a value of the statistical life, in other words, the notional life that can be

saved if one takes a course of action, and you say, well, if -- we will spend up to $8 million to save a life, but we will not spend any more than that, and that is something which NICE absolutely does not do and that is why it is outside your expertise because NICE does not do it.

A. Yes, NICE does not have a value for this either explicitly or implicitly.

THE PRESIDENT: Indeed, thank you very much.

A. Next slide, please {XC3/1/18}.

So now we are moving on to our cost effectiveness criteria. This is for guidelines, as I have already said, technology appraisals, we seem to be flipping between the two, they have a threshold of between 20,000 and 30,000, but, as I have already said, below £20,000 per additional QALY is generally considered to be cost effective; more than £20,000 per QALY not usually recommended, but we do recommend things that are more than £20,000 per QALY when there is a strong case that it would be an effective and efficient use of NHS resources.

I think it is important to point out here that the ICER is not the -- whilst it is NICE's main consideration, its main decision rule, it is not the only consideration in decision-making, and I have taken

this diagram on the left straight from our committee slides which we present to the committees whilst we are inducting them, and that puts in some of the other things that we have -- that may not be captured in this threshold. So I think really if you look in the east of that diagram, that is the benefits not captured, that is quite relevant for technology appraisals. Often these are newer interventions, the randomised control trials have only been going on for one or two years. When you extrapolate past those two years in your economic model, you tend to be conservative, you take a conservative estimate, you do not know what is going to happen, but they may say that actually those QALYs you get after those two years have not been captured adequately, so that is an underestimate.

The south and the west bits, that is the innovative nature of the technology and the health inequalities, I am not sure how much phenytoin comes into those ones, I have not mentioned health inequalities in my economic evaluation, I do not think Dr Skedgel mentioned it in his, I do not think it is really a consideration here, I think importantly is this one in the north which is the uncertainty in the evidence. NICE are risk-averse, so we want strong evidence underpinning our recommendations ideally. Certainly as we get closer to

£20,000 per QALY threshold, you want stronger and stronger evidence to support that.

Next slide, please {XC3/1/19}.

So I will just quickly go through the NICE guidelines in 2012 and 2022. Next slide, please {XC3/1/20}.

This is just in table form what was recommended for add-on therapy for focal seizures in the 2012 guideline and you see first line we have these list of drugs that are recommended and then you have the second line there, and I have helpfully circled phenytoin, and then the ones in yellow are those ones from Dr Skedgel's comparator set in his economic evaluation: perampanel was not included in the 2012 guidelines so it is not in this list, but he has essentially, as he says in his report, he has compared phenytoin to the other drugs that were recommended, second line, in the 2012 guideline.

THE PRESIDENT: Thank you.

A. If you go on to the next slide, please {XC3/1/21}.

As I said yesterday, I was not involved in the 2012 guideline, I have gone back and inspected the documents, so my knowledge is entirely from what was in the public domain anyway.

But we took a -- they took some approach in 2012 to

what we later took in preparing the 2022 guideline, that they did a systematic review and an economic model. A systematic review is where the committee will set what they want to look for in the evidence, they will set what type of evidence they want to look for, in this case they only wanted to see randomised control trial evidence. They will set the population which is people with focal seizures eligible for add-on treatment, and then set their interventions in comparison to what drugs they want to look at and then also their outcomes, what outcomes they want reported in the randomised control trials and then we will look for the evidence based on that and we will present that to the committee and then we will build an economic model based on that.

I think a major difference between the 2012 guideline and the 2022 guideline is that their evidence into the economic model and to inform the committee of their decision was based on pairwise analysis, that is the direct trials. They did try and do a network meta analysis, but the first consultation they sent that out to stakeholders, it was later dropped following a number of comments, but the final published one it was just pairwise analyses.

So that presents a lot of difficulties in add-on therapy, because most things are compared to placebo.

We are not really interested in things are better than placebo, we want to know what is the best active treatment, and I think that was -- if I can criticise the 2012 guideline, I do think that was a weakness of the 2012 guideline that they did not do that, they did not carry on with that network meta analysis.

Phenytoin was excluded from the economic model due to its -- and I am just going to quote this because it is a medical term so I do not want to go into too much detail on it, but because of the narrow therapeutic window which made it difficult to administer, but even though it was not in the economic model, the committee are still told to consider the -- they need to weigh up the costs and the benefits of any intervention they recommend, even if it has not gone through an economic model, so that would have still been a consideration of the committee even in an informal way, and as we did in 2012, in 2022 they only found one very low quality trial showing no difference of phenytoin versus tiagabine, and that was in the outcome of 50% reduction in seizure frequency and treatment withdrawal due to adverse events and I am going to discuss that trial a little bit later because I know we have had a little bit of back and forth on it.

Next slide, please {XC3/1/22}.

So the 2022 NICE guideline, again, we revisited the 2012 guideline to see what they did there, well I thought they did badly there and what we could do better and it was decided that we should do a network meta analysis and we also looked at the cenobamate TA that was in development as the NICE 2022 guideline, so we wanted to see what they had done there and what the Evidence Review Group said was good and what was bad about that.

As we said when designing our systematic review we need to pick the outcomes that we want to look for, and the committee, which is made up of the medical professionals and patient/carer members, as their critical outcomes they put greater than 50% reduction in seizure frequency and seizure-freedom, and we make a point at NICE when we are picking the outcomes of a model that we ask the patient/carer members: are these things that are really important to you. So if I give the example of -- I am trying to think of a good example? It is probably not a good example: I will give the example of menopause. Often consultants are interested in Ph levels, when actually people want to know if it is painful when they go to the toilet, whether it is painful when they have sex, so it is really important that you do ask -- that the

patient/carer members are involved in that and it is not just the clinicians leading on that, so that was recognised by the patient/carer members as an important outcome.

I think I have already said this, but we are interested in comparisons between active anti-seizure medications. I use ASMs, I know you have been using AEDs throughout, they are interchangeable.

They decided to do that because as I have already said, we do not really care if these drugs are effective compared to placebo. We want to know what is the most effective active medication, and the only way to do that given that most of the trials were compared to placebo was through a network meta analysis.

The committee were very insistent on this, this was not led by me, they wanted a blank state in terms of lines of treatment. If something was effective in terms of reducing seizures, if it was well tolerated in terms of adverse events and it was an acceptable cost, then they felt that any treatment could be at any line for these add-on treatments including phenytoin.

Some of these anti-seizure medications were not included that we looked at in the network meta analysis were not included in the economic model, some of them were not readily available and licensed in the UK,

ie retigabine which I think was withdrawn over safety concerns, but we put it in anyway to increase the amount of observations in our trial, and we also removed the -- we did not look at cenobamate in the economic model, because that was covered by a TA, so we could not -- a technology appraisal, so we could not update that, we had to accept the technology appraisal because they take precedence over the guidelines, and we also did not look at placebo, because there was no -- we were never going to recommend placebo, we do not recommend placebos at NICE.

But all other interventions that had evidence in either the 50% -- greater than 50% seizure reduction meta analysis or the seizure-freedom network meta analysis were included in the economic model, and, as I have already said, we have included phenytoin this time. The committee this time decided differently to the previous committee in that it should be in the economic model and that the narrow therapeutic range should not be a barrier to it being recommended.

Just because this is probably important, the drugs costs we used for phenytoin were those from the BNF in March 2021 and it had phenytoin at £11.08 for 28 100mg tablets.

Next slide, please {XC3/1/23}.

These are our results. I was a bit reluctant to present these because they are base case results and there is a lot of uncertainty in our model, but I thought it would be odd to do the presentation without it, and I have helpfully highlighted in yellow phenytoin and all the comparators that Dr Skedgel had in his comparator set, and you can see they are ranked by their cost effectiveness, and you can see that actually in the base case results, phenytoin comes in second of all those treatments compared to pregabalin.

I was going to do a slide on the uncertainty around all this, but there is 15 interventions, there is loads of lines, it is really hard to follow, I was conscious we only had 30 minutes to do this, but just mark my words, there is a lot of uncertainty around these, you cannot put a lot of -- or NICE and the committee do not put a lot of confidence in these results that they were within the ballpark of what they should be, there is wide credible intervals around these estimates.

Just to show how NICE came -- how the NICE guideline committee considered these, just keep an eye on lacosamide. That has done really badly in the base case results, you can see it is in 16th place out of 17, but when I compare it to the recommendations on the next slide, you can see how that has fed in.

Next slide, please {XC3/1/24}. Sorry, I will show the recommendations on the slide after.

So these are some of the considerations of the guideline committee when they were making these recommendations, and these are all documented either in evidence review F or the economic model write-up, both of which are in my evidence bundles.

So, firstly, NICE's key outcome measure which is the ICER, we have converted it into incremental net monetary benefit here by converting the QALY side of it into a £20,000 per QALY value, so that is the results of the economic model, so they considered that on the previous slide and the uncertainty around that. As I already said, there was large credible intervals around those estimates.

They considered just the effectiveness evidence, that was the results of the NMA, how did the interventions compare to each other, because you could compare them indirectly, which is what they wanted to do, they wanted to compare active treatments to other active treatments, they did not want to compare them to placebo.

They looked at the results of the direct trial comparisons, they went back to the individual trials when they were high quality. Unfortunately they were

usually to placebo, but we did have a few trials that compared active treatments, but they tended to be lower quality and smaller, which was disappointing, but that was the evidence that we found.

We also looked at the individual risk of bias of the studies. If there was a high risk of bias of the studies that informed an intervention, then we can put less confidence in those results.

Also the age of the trials, I think we had trials going back to 1970 in our analysis, we want to give less weight to the older trials than you do to the newer trials because all the background treatment changes, all the follow-on treatment changes.

I should put this higher up, really, but patient choice. These interventions have quite complex adverse event profiles and they are different between the drugs, but they are also different to how patients would choose between them or how they would impact on their quality of life. The example I always give that if you are a young female you may be more averse to hair loss than perhaps if you are an older male. So it is important to have that patient choice there. We did not want to just recommend the most cost effective drug and then second-line, the second most cost effective drug and then the third-line, the third most cost effective drug.

We wanted a choice at each line, and that was consistent with the 2012 guideline where they did have multiple treatments at each line.

We always say at NICE the least cost effective drug is the drug that people do not take because you get all of the costs ends up sitting into a drawer, it is sitting in a drawer, you do not get any of the benefits of it, so it is important that people can tolerate these drugs and that they are effective and that is more likely patients have a choice, they can discuss their adverse events, they can alongside their doctor, pick the most appropriate treatment for themselves.

I have already covered the adverse events profiles, and this is kind of a catchall, it is the experienced opinion of the guideline committee. These are people who have lived with the condition of epilepsy or people who have been treating epilepsy sometimes for decades, so they see things that are not going to be captured by the economic model, they can add that contextualisation to the economic model. We do not call these consultants in from the hospital to tell us if 19,000 is less than 20,000 or 21,000 is more than 20,000, we are quite capable of doing that by ourselves, these ICERs need that contextualisation and the uncertainty needs that contextualisation and where this -- we can kind of

capture the -- we can kind of -- we can capture the statistical uncertainty but all these structural uncertainties and the uncertainties around assumptions, that is quite hard for us to capture in a numerical way. So that is just things that the committee considered in addition to the ICER.

So next slide, please {XC3/1/25}.

So here is what we recommended, and this was recommended by the guideline committee based on the economic model and the network meta analysis, and this was also put out to hundreds of stakeholders who were able to comment on it and refined it as such.

You can see these are the ones in yellow are the comparators from Skedgel's comparator set and we have come to different conclusions to Skedgel. You can see that lacosamide, I told you to keep an eye on that, that did really badly in the base case economic model, but we went back and we looked at it, based on their clinical experience, it did not match up with what they saw in practice, and from the randomised control trials we seemed to have a very high withdrawal due to adverse events which meant people were going on to it and then dropping out very quickly, so you were getting a lot of the costs, but you were not getting a lot of the benefits, and that was a lot higher than other

treatments in the -- with the 17 drugs that we compared in the economic model, and the committee did not think that was clinically plausible based on their clinical experience, etc, they thought that was an overestimate, they thought there were problem weaknesses in the trial, they had been a bit too cautious in withdrawing people, and, therefore, when we lowered that, the withdrawal due to adverse events, it was much more cost effective, it went up, and that is why even though it came 16 or 17 in the base case we have recommended it, or we have not, the committee have recommended it first-line and it has gone through stakeholders who also thought that was the appropriate place for it.

Then in the second line here we have also got eslicarbazepine, perampanel and pregabalin, they are also in Skedgel's comparator set, but from the guideline committee based on their effectiveness and cost effectiveness they thought they were better options than phenytoin, and the only one where there is kind of that equivalency with those in Skedgel's comparator set is with vigabatrin where they have been recommended third-line.

For me, phenytoin has been demoted in this from the 2012 guideline where it was an option as a second-line treatment, it is now a third-line add-on.

Next slide, please {XC3/1/26}.

So I already just said this point: it has dropped from second-line to third-line add-on from the 2012 guideline.

The NMA estimated an odds ratio of 1.97. Varies above 1 show it is effective compared to a placebo, varies below 1, less effective than placebo for a 50% reduction in seizure frequency, that is for phenytoin. If we can see wide credible intervals that passed the line of no effect we do not have any great certainty that it performs better than placebo. So it is more effective than placebo in the base case, but we do not have great confidence around that.

There was no evidence identified for seizure-freedom in the literature review, I am going to discuss that later, because that is a point of contention that has come back and forth about how we estimated the effectiveness of phenytoin for seizure-freedom.

It is a point I have already made: even though it was 10th of 17 anti-seizure medications in the base case, we did actually recommend it quite -- we recommended it third-line with brivaracetam, perampanel, eslicarbazepine and lacosamide, all seen as better options based on their effectiveness and cost effectiveness.

Next slide, please.

I want to point out some of the key differences between the NICE and the Skedgel approach.

Next slide {XC3/1/28}.

So there is a number of differences in the approach in the assumptions made, I am going to outline a few of them in the next slide, it is not intended to be exhaustive. I have concentrated on ones where I feel the NICE guideline has either been misrepresented and/or unfairly criticised.

There continued to be some confusion even after my two statements about exactly what I have done so I am going to try and clear some of that up.

Just to be clear, I am not trying to mirror the full forensic appraisal of the Evidence Review Group. I have stuck on bits where the NICE guideline model has -- where the NICE guideline model has been criticised and I have responded to them. I have not done a full review of the model as an expert witness would have done, and nobody has asked me to do that.

The following slides, they give records of the committee's opinion at the time where they decided to go with the approach that they did, it is not me giving opinions -- it is not me giving opinions today.

I think the two key things to discuss to explain the

key differences are the use of the three state model which NICE did in 2022, compared to the two state model which Skedgel has done in his expert report, and also the inclusion of this Cramer trial.

So next slide, please. {XC3/1/29}.

So I have just tabulated the differences here. So on the left you have the NICE 2022 model, on the right you have the Skedgel model. So we had a much wider comparator set, we had all 17 anti-seizure medicines, consider we wanted that blank slate, wanted to look at everything again. Skedgel has only looked at the third-line ASMs from the 2012 guideline. We have done it at the prices -- the most recent prices that were available at the time, which were 2021 prices for the drugs and 2020 prices for the other healthcare expenditure because our guideline committee were making recommendations for that time period. Skedgel has done 2012 -- has asked kind of the question if you had the 2012 prices in 2019 what would you conclude in terms of cost effectiveness, so his drug prices are from 2012, his downstream healthcare expenditure costs are from 2019.

Then we have the three state and the two state model which I am going to go on to in more detail in the next couple of slides.

I have not got a slide on this, but I think this is really important. We had different discontinuation by anti-seizure medication in our economic model, so based on the withdrawal due to adverse events from the randomised control trials that informed the input in the economic model.

Dr Skedgel had the same discontinuation for all anti-seizure medications, and I point this out because this was a criticism that was directed at me by Professor Walker, so I just wanted to say that actually we did look at the effectiveness, reducing seizures, and also the tolerability, do people stay on the drug, in our economic model.

These next two -- we adjusted for the differences in placebo response, the response to placebo changing over time, Dr Skedgel did not do that. We pulled all treatments together regardless of dosage; Skedgel treated different dosages as different interventions. We do disagree on that, but I think it is probably a genuine debate this, so probably not appropriate to go into more detail in that in the teach-in, but I am happy to address it during my cross-examination.

Also the NICE model had low estimate of costs following treatment failure, Skedgel had higher estimates of costs following treatment failure, but

I think that is probably a fair difference. Dr Skedgel's model is further along in the treatment pathway, these patients are starting to run out of options, so they will probably move on to surgery much, much sooner which is a very high cost. I think that is probably a reasonable difference in our assumptions in the model, but I think this is really the key one at the bottom, we make very weak/moderate conclusions from our economic model, we do not put great confidence in them at all, and that is a result of the evidence that is underpinning it rather than anything inherent in the economic model, whilst Dr Skedgel makes quite strong conclusions based on the evidence and based on his economic model.

Could I go on to the next slide, please {XC3/1/30}. So I am going to discuss the Cramer 2001 trial now and the two state versus three state model.

Next slide, please, {XC/1/31}.

This is very simplistically the two differences in the structure of our model. So Skedgel essentially had two states in his model: he had either a complete response, you end up seizure-free, or you do not have 100% seizure-freedom and you are looking at that no response state.

We split it into three, so we would have those

people who had complete seizure-freedom informed by the network meta analysis on complete freedom, we had this greater than 50% reduction in seizure frequency informed by the network meta analysis on greater than 50% reduction in seizure frequency and we also had this less than 50% reduction in seizure frequency.

Those two states combined would be the same as the no response state in Dr Skedgel's model. We had that extra level of granularity in there. I will explain why the committee thought that was important in the next slide {XC3/1/32}, if we can have the next slide, please.

So why did the committee decide on the three state model? I think we have agreement here that seizure-freedom is the most clinically important outcome in this, it allows people to drive again, which is one of the big concerns that our patient/carer members pointed out, but it is a reasonably rare event, it is difficult to -- when you have a rare event, to get a randomised control trial that is sufficiently powered to detect a difference you need more people within it, so they are often very difficult to recruit to, so when they are done they very rarely find a difference and I think most of the trials in this area showed no difference to placebo and that wasn't because these drugs are not effective, it is because the trials were

too small to detect that difference.

So consequently, most trials have greater than 50% seizure frequency as their primary outcome, that is what they will power their randomised control trials to. When they are looking at a number of people to recruit to their randomised control trial to detect a certain size difference they will power than on greater than 50% seizure reduction rather than seizure-freedom.

THE PRESIDENT: You may not be able to answer this, Mr Hawkins, and do say if you cannot, but given that the gold standard for the treatment of epileptics is seizure-freedom, as you have said, and given that the stable regime is rather important so that if you have something that works you do not want to move away from it, how do you conduct these trials given that you will be substituting, I assume, for an active ingredient, a placebo, and thereby exposing the patient to the risk which of course you are trying to quantify of a seizure?

A. My understanding is that you are adding to the background treatment and active treatment or you are adding to your background treatment a placebo, so you are not giving them a placebo, you are giving them whatever their current treatment is plus placebo versus current treatment plus an active anti-seizure medication.

THE PRESIDENT: I see. So given that sodium phenytoin is a longstanding form of treatment which will be offered as a continuous form of treatment to those patients who are on it, you will not be substituting them away from sodium phenytoin; you will be calibrating other forms of treatment that they are not getting?

A. So my understanding is people add on to their treatments, they withdraw some treatments from it, I cannot say --

THE PRESIDENT: If you cannot say, do say, because I appreciate I am on the very fringes of your expertise because we are moving into medical matters, not evaluative matters that NICE does.

A. But people do add treatments, they do remove treatments when they get to this stage, but I cannot say any further than that, you would have to ask a medical expert.

THE PRESIDENT: I see.

A. As I said, it is still an important outcome to patients, this greater than 50% reduction in seizure frequency, that was the 2022 guideline committee's opinion. The NICE 2022 utility value said that, if you look at our utility values in our economic report, and it is also in Skedgel's utility value, so if you look at the volume of less than 50% reduction in seizures compared to greater

than or equal to 50% reduction in seizures, if you look at the top right of my slide there you can see there is a 6 percentage point increase in your utility value there, so there is an increase in quality of life as a result of reducing those seizures in the utility values in Dr Skedgel's model, and there is a large amount of evidence on this outcome. We found 99 randomised control trials in 27,686 participants. That is a lot of evidence to just ignore.

I think it misses a lot of the benefit of the drugs. The highest complete response rate in Dr Skedgel's model was 7%, that was the highest that came out, so you are saying there is no benefit of these drugs for over 90% of the patients, and I suppose the question you are going to have to ask yourselves is does this adequately capture all of the benefits of phenytoin and its comparators and therefore have they been properly compared?

I think it is important to point out the Evidence Review Group in cenobamate favoured the three state model. These are the referees of the technology appraisal process, and this was their opinion, that that was the better model.

Next slide, please {XC3/1/33}.

So the Cramer 2001 study. This was included in both

the 2012 guideline and the 2022 guideline. As I have already said, we undertook a systematic review where the guideline committee asked us to report -- to show them any randomised control trial that showed a greater than 50% reduction in seizure frequency as an outcome, and Cramer 2001 met the committee's inclusion criteria. They wanted to see it.

I agree there is a high risk of bias in the study, it is not a great study, it is not a large study although it is bigger than some of the studies that Dr Skedgel has used in his network meta analysis, and actually it favoured phenytoin over tiagabine. It was not statistically significant, it was not particularly strong, so it did not strongly favour it, but if anything you are removing favourable evidence for phenytoin by not considering it, even though that is very weak and you probably do not want to give it much weight. It is the best or only, depending on how you want to look at it, randomised control evidence identified on phenytoin as an add-on anti-seizure medication, so it is either that randomised control evidence or no randomised control evidence.

There seems to be some confusion about how Cramer fitted into the economic model. I just should say that it was part of the greater than 50% reduction in seizure

frequency network meta analysis that NICE did and the outcomes from that network meta analysis informed the economic model, so it was feeding into phenytoin -- into the economic model through that 50% reduction in seizure frequency, so we have made no assumption around greater than 50% reduction in seizure frequency for phenytoin in the economic model, we have taken it straight from the randomised control trial evidence.

Next slide, please {XC3/1/34}.

Just to say we have identified Cramer 2001 as having a high risk of bias. These are all the randomised control trials that Dr Skedgel included in his network meta analysis, and this is not a criticism of Dr Skedgel because I have used these same studies in my network meta analysis, but we were both quite happy to use randomised control trials which had some risk of bias, and randomised control trials which had high risk of bias, so it is not that we are only including the really top tier evidence, the randomised control trials with low risk of bias, we have had quite a wide net, so we were quite -- both quite happy to use quite low quality randomised control trials in our network meta analyses.

Next slide, please {XC3/1/35}.

So we get on to this phenytoin seizure-freedom, and this is me capturing the committee's view on this, it

will not necessarily be mine, we put -- as I say, the economic model is not a black box, we put every assumption to the committee, they agree every assumption, there is nothing that goes into the economic model that they are unaware of, and, as I have already said, the protocol for our systematic review, what evidence we are going to look for, what outcomes we are -- what evidence we are going to look for, the committee were only interested in randomised control trials, which seems reasonable, there are over 100 randomised control trials in this area, do you really want to start looking at the lower quality evidence, your observational studies, your case control series, do you want to give a lot of weight to those when there is all this other evidence for the other 15, 16-odd anti-seizure medications. So I wanted to avoid those other study designs that provide weaker evidence.

PROFESSOR WATERSON: Just to check, these randomised control trials that you are talking about, are these double blind trials?

A. Yes, they are all double blind.

PROFESSOR WATERSON: Thanks.

A. As I said, this is an evidence-rich area, there is over 100 RCTs, how much weight do you want to give to interventions that do not have that randomised control

trial evidence and how much -- if we do use inputs other than randomised control trial evidence do we want to give great weight to those results, and I do not think the committee wanted to. These are pharmaceuticals, you really do want to have randomised control trial evidence underpinning them.

The other thing to point out is, as I have already said, it is hard to power these randomised control trials to look for seizure-freedom, and actually, the majority of the seizure-freedom randomised control trials showed no difference to placebo, and that is probably not because they are not effective compared to placebo, it is because we have not recruited enough patients, so it seemed unfair to give something without randomised control trials a higher weighting than those ones that have shown no difference to placebo in the randomised control trial evidence.

Again, it is kind of making the same point a different way: there is many different anti-seizure medications, there is a lot of options for patients in this area, do we really want to make strong recommendations without that RCT evidence?

It was the committee's assumption, not mine, that it was conservative to assume no difference to placebo for phenytoin, and I do not think that is a best estimate,

that is a conservative estimate that there was no randomised control trial evidence, and just to say that we did give it a wide probabilistic sensitivity analysis to reflect that uncertainty in the absence of evidence, so we have essentially said with that wide distribution of probabilistic sensitivity analysis, that we do not know, nobody knows, that we have not got that top tier randomised control trial evidence, so we have not given it zero and then kept it fixed on that or very narrow range when we have done the probabilistic analyses, we have said we do not know.

Just to point this out because it has been said a few times that we assume that phenytoin was no better than placebo, we did -- obviously the total QALYs for phenytoin, that is also fed into by the greater than 50% seizure-freedom outcome for that network meta analysis. That had a positive result for phenytoin. That allowed -- so in the economic model as a result of that, phenytoin had more quality adjusted life years than placebo, so we are saying it is more effective than placebo.

Next slide, please {XC3/1/36}.

So I am going to talk about Skedgel assumption for seizure-freedom and why we did not go with a similar approach.

I think it is important to point out this is the most important input to Skedgel's model, it is the key driver of all Dr Skedgel's conclusions, so the weight you put in that is essentially the weight you can put into his conclusions, and he has come up with the large estimate compared to his comparators of seizure-freedom has done quite well in his estimate, it is significantly different to placebo, his confidence intervals around his estimate do not pass the line of no effect, he is saying with some certainty that phenytoin is better than placebo, and that is extrapolated from randomised control trial evidence in the monotherapy population from the Bill 1997 trial but I think it is important to point out that that is not the same as randomised control trial evidence. Once you extrapolate from randomised control trial evidence it breaks the experimental component of randomised control trials. That is not in the same tier anymore as randomised control trial evidence.

So it is important that these estimates from the hypothetical randomised control trials are not treated or interpreted as randomised control trials, and I think that is particularly important because it is treated as a randomised control trial in Skedgel's network meta analysis, which breaks a number of important assumptions

of network meta analysis.

In short, it overestimates the precision around it. I have kept out the slide with all the matrix algebra in explaining that, but I will be happy to get my matrix algebra out in my cross-examination if we want to explain why that is a really bad thing to do.

I think it is important to point out it is measured in a different way to the comparators, it is not a randomised control trial, it is a -- I call it expert opinion, I think Professor McGuire has called it a narrative summary, but it is not a randomised control trial, it is different, it is lower down on the evidence hierarchy, and I am going to show you the evidence hierarchy in the next slide.

So I would argue actually we are just at different point estimates on a wide distribution of expert opinion, we have not really made a different assumption at all, we have just done a different point on a very, very wide distribution, and, as I said, I was expecting some questions on that but I will not comment on the clinical plausibility of any estimates, because that is outside of my expertise, it might be a good estimate, it might be a terrible estimate, it might be similar to what an expert would estimate for this but I am not going to comment on that.

Next slide, please {XC3/1/37}.

So this is the evidence hierarchy, everyone who has worked in evidence-based medicine has seen a version of this, they do change slightly, but they all have the same essential theme.

At the top you have got your critical appraisal which is your systematic reviews, your meta analysis where you combine all this evidence together and you have given it some sort of critical appraisal to come to some kind of combined outcome using all of the evidence that is available, and then below that you have got your experimental study designs, ideally you want your double-blinded randomised control trials, that is your best of your non-systematic reviews and meta analysis things and then as you go down this hierarchy you end up with lower and lower quality of evidence, your non-randomised studies, your observational studies when you see what has happened with people who have taken a drug and those people who have not taken a drug and the further you go down this hierarchy the less confidence you can place in your estimates from those sources.

PROFESSOR WATERSON: Can I just check, so these Cochrane, I think they are called, studies --

A. Yes.

PROFESSOR WATERSON: -- where would they fit into this picture?

A. Well, Cochrane, rather big headed of them, they have their own version of this evidence hierarchy and they are the top triangle, Cochrane reviews, and then they put meta analysis and systematic reviews below that, so in their own opinion they would be the top triangle right at the top of that.

THE PRESIDENT: Where would you put them?

A. I would agree they do do very good work, they would certainly be in the top triangle, I would like to put my own work alongside them, but I will let them disagree with that.

I think it is important this is not just for Skedgel's analysis, this is my analysis, at least for seizure-freedom. The comparators are from a meta analysis, a network meta analysis of randomised control trials. The estimate around phenytoin is not from a randomised control trial. So we have measured them differently, there is different quality of evidence around those inputs to the model.

Next slide, I think I am almost finished now.

Thank you, I have not done a summary slide because I was not sure what questions you were going to ask or what you were going to find interesting or what I needed

to highlight, but I am happy to ask any questions or revisit anything.

THE PRESIDENT: No, thank you very much.

Thank you very much. We have asked our questions in the course of your presentation.

A. Thank you.

THE PRESIDENT: Thank you very much for that helpful teach-in. We will let you go. You are not released from the witness box, you will be coming back, but do sit down and listen to the other teach-ins. Thank you very much.

A. Thank you.

THE PRESIDENT: Mr O'Donoghue, just before we get to the next teach-in, may I ask who is going to be cross-examining Mr Hawkins, will that be you or will that be Mr Johnston?

MR O'DONOGHUE: It will be me, yes:

THE PRESIDENT: You will be bearing in mind that Mr Hawkins is a witness of fact, not an expert, in your cross-examination.

MR O'DONOGHUE: Indeed, indeed.

THE PRESIDENT: Because I can imagine there will be a great deal in his evidence and indeed in his teach-in that you will be wanting to put, and he may -- I do not know how quickly, but he may come to the limits of his factual

understanding, the extent to which he can do no more than say: this is what NICE has done, and I can assist no further.

MR O'DONOGHUE: Indeed.

THE PRESIDENT: At that point, I will expect your cross-examination to stop.

MR O'DONOGHUE: That is entirely fair, and indeed, you will recall, sir, from the pre-trial review that we made a virtue of the point that he is a factual witness and not an expert witness, but there are, sir, obviously a couple of points in that context that we need to put to him.

THE PRESIDENT: No, I am not trying to shut you out, what I am trying to establish is the ground rules in this case because if, as may well be the case on a number of these slides, he is going to say: well, this is what NICE has done but I cannot say anything more because I did not do it, then if you were an expert I would expect you to go further as to why he is putting this forward and why he or she cannot speak to it. In this case, because we quite understandably do not want to have a whole bevy of NICE factual witnesses coming in because time is what it is, as I say, you will at that point move on to another matter.

MR O'DONOGHUE: Yes.

THE PRESIDENT: And we will consider what weight we can attach to the bare document in the absence of a witness able to speak to it.

MR O'DONOGHUE: Yes.

THE PRESIDENT: I am not saying that you will not be able to say that there are certain limits to what we can draw out of the material that Mr Hawkins has adduced; it is just I do not want that point or that sort of point being put to him because he is explicitly not here as an expert.

MR O'DONOGHUE: Of course.

THE PRESIDENT: I am grateful.

MR O'DONOGHUE: That is very fair.

Sir, one flipside of that point of course is that there are points made in relation to NICE both by Professor McGuire and Mr Hawkins and I will not be putting that twice to the two witnesses.

THE PRESIDENT: That is understood.

Ms Morrison, you do not have anything to say in the light of my indication to Mr O'Donoghue as to how the cross-examination of Mr Hawkins should proceed?

MS MORRISON: No, sir. I think we have been very clear in how Mr Hawkins is intended to be used. It is simply to give the Tribunal as much help as possible --

THE PRESIDENT: That is right. I am merely wanting to

ensure that the ground rules of cross-examination are understood in what is a slightly unusual situation because this is factual evidence, but it is kind of not.

MS MORRISON: Sir, the only reason I rose is just on that latter point that Mr O'Donoghue said: look obviously if they are saying the exact same thing Mr O'Donoghue does not need to put the same thing to two witnesses, one expert and one not, but of course, Professor McGuire goes much further in his discussions so of course for most areas one would anticipate there would be questions for both on any common topics in any event.

THE PRESIDENT: I am sure Mr O'Donoghue will take his course, but we do not need the same point put twice where it is going to be simply a re-traversing. If, of course, the witnesses have different views or different approaches, then the same question will have to be put.

MR O'DONOGHUE: Indeed. Sir, in a sense, it is more than that, because Mr Hawkins is from NICE, he was involved in the guidelines in 2022, he is obviously best placed to speak to what they did or did not do.

THE PRESIDENT: Indeed. Thank you.

We will move on to the next teach-in.

MR O'DONOGHUE: Dr Skedgel.

THE PRESIDENT: Thank you.

DR CHRISTOPHER SKEDGEL (affirmed)

THE PRESIDENT: Thank you very much, Dr Skedgel, do take a seat. I think you have some water and a glass, and I hope your materials that you will need for your teach-in.

I will hand you over to Mr O'Donoghue.

Examination-in-chief by MR O'DONOGHUE

MR O'DONOGHUE: Dr Skedgel, we have expedited swearing in, so I will not hang around.

You have given two reports in these proceedings. Your first report is at {XE3/1}. Your second report is at {XE3/2}. Do these two reports, Dr Skedgel, reflect your true and complete professional opinion to the best of your knowledge and belief?

A. That is correct, yes.

MR O'DONOGHUE: Thank you, Dr Skedgel.

Teach-in by DR SKEDGEL

DR SKEDGEL: Thank you very much. I understand I will be giving a health economics teach-in that I think will cover much of what Mr Hawkins covered and perhaps some of what Professor McGuire is going to cover as well, but hearing it in three different perspectives is probably helpful.

THE PRESIDENT: Thank you.

A. Can I have the next slide, please {XE7/8/2}.

A little bit about my background. I have a PhD in health economics and decision science in the University of Sheffield. I have been working in health economics and health systems research since 1996. I would estimate that I have developed probably 30 economic models over the course of my career including in areas of cancer, multiple scleroris, influenza, liver transplantation, haematology, and now, epilepsy.

It is probably worth noting I have also, prior to being in consulting, was in academia and lectured in health economics.

Next slide, please {XE7/8/3}.

I am a director at the Office of Health Economics, it was established within the Association of British Pharmaceutical Industries in 1962, arguably making it one of the oldest health economics consultancies in the world. We are organised as a charity with a mission to support better healthcare policies by providing insightful economic and statistical analyses of critical issues.

We are also a designated and independent research organisation by the UK Research and Innovation, a body of the UK Government that directs research and innovation funding. This designation means we can compete with universities for government grant funding.

As part of this designation we commit to upholding the highest standards of research and rigour and integrity in all of our research.

Next slide {XE7/8/4}.

My instructions: I was asked to develop a health economic model to assess the value of phenytoin to the NHS at the time of its 2012 price change. To execute these instructions, my team and I used standard health economic modelling methods, including those recommended by the National Institute of Health and Care Excellence and other well-regarded health economics texts.

I also used the recent cenobamate model submitted to NICE as a template for the model that I will describe here.

Next slide, please {XE7/8/5}.

So a quick overview of health economic evaluation and my view of how NICE fits into that decision problem.

{XE7/8/6}. So what is health economic evaluation? It is a distinct form of cost benefit analysis applied especially to resource allocation decisions in healthcare. As part of this cost benefit analysis, it seeks to estimate the value of a health technology to the healthcare system. In seeking to achieve this goal, it departs from conventional cost benefit analysis by largely rejecting willingness to pay or continued

valuation, whatever you would like to call it, as the only appropriate or even the most appropriate measure of value.

As Mr Hawkins pointed out, health economics tends to favour the quality adjusted life year as a measure of value in health technology.

Next slide, please {XE7/8/7}.

Briefly a visual illustration of how the QALY works and how we estimate the change or the gain in QALYs between a comparator and treatment. If we think of health in two dimensions, the quality of your life at a given time and the length of your life, the main advantage of the QALY is it lets us understand both of those dimensions in a single summary measure.

We can assess the quality of life of a patient or a group of patients at any point in time and we can assign some weight to their survival according to that quality of life in percentage terms. Everything is measured relative to a state of perfect health, which, in itself, is perhaps difficult to define. To follow up perhaps on your comment yesterday: quality of life within the QALY is a subjective measure. There is no objective way to say what I consider perfect health is the same as what you consider perfect health. The goal of health economics is to try and arrive at a robust,

reliable, reproducible estimate or perhaps central estimate of how people in a particular health state would describe their health on a scale of 0 to 100 on any given day.

So I am very happy to go into that discussion, or --

THE PRESIDENT: Well, are you otherwise planning to move on to a new slide, because I do have a question in relation to this, but I want you to finish your exposition on this slide before I do.

A. I am very happy to go into the details of the QALY. The only next thing I was going to say is how then we would consider the gain in the QALY as the difference in estimates between before and after --

THE PRESIDENT: Well, that was exactly what I wanted to ask you about, the before and the after.

You will have heard my questions to Mr Hawkins regarding, as it were, old and new. Would it be right to say that your comparator equates to the old and the treatment equates to the new?

A. Yes. So we in this context -- comparator is defined very broadly: it can be no treatment at all, which does not mean no healthcare at all, but it can mean no active treatment at all. In a no treatment, you may still, presumably in the context of epilepsy, an untreated person with epilepsy will have A&E admissions, they will

visit their GP quite often, they may visit a specialist, so even in the absence of an active treatment they will still be accruing cost to the NHS.

So that no treatment comparator can be the baseline for the analysis.

THE PRESIDENT: I understand, but you are, in exercising this comparison, this old versus new, you are looking to a very specific malady or ailment, here epilepsy, and you are saying: well, here is the present state of the patient, this is the quality of life that is obtained through this form of treatment or non-treatment -- I quite accept your point about that -- and then we have the new, we have the treatment box and what you are doing is you are saying: well, how does this situation change if one introduces this new element, whatever it might be, and we ask ourselves what the difference is in terms of comparative cost and comparative QALY benefit or disbenefit.

A. Precisely. We do not try to approach it in a ledger sense and say: well, you know, this thing will be lower and this thing will be higher and we can sum across those changes. We try and measure in the aggregate: what is the aggregate of health utilisation, health expenditure, in this state of the world and if we change the state of the world by adding a treatment, what is

the aggregate in this state of the world, and what is now the difference between those states of the world in terms of cost and in terms of QALY outcomes.

THE PRESIDENT: Again, let me read that back to you and you can tell me how far I have got it wrong: you do not take a siloed approach to the data, you take an holistic approach, and your new versus old approach is holistic in that sense?

A. Holistic is a very good word, yes.

THE PRESIDENT: I am grateful.

A. So once we have measured your quality of life, using standard methods -- to me, this is the thing that distinguishes health economics from the other branches of health economics: that we use an explicitly subjective measure of someone's health-related quality of life.

We have standard methods, it is obviously a central area of research within health economics: what is the best way to ask someone to define their health.

We try -- we ask that question by asking people to make a trade-off. Mr Hawkins began describing the time trade-off, so we would say: imagine you can live for ten years in your current health state or there is a magic box you can walk through and it will cure you but it will take some years off of your life. If you could

have ten years in your current health state or five years in a state of perfect health, would you make that trade? The lower the number of survival in the second scenario, the higher the implied severity of your condition, the less desirable the state that you are currently in.

So by using those methods, we can estimate the quality of life in any period, and then we sum across those periods to say: this is your QALY profile in any particular health state, and then we can estimate how treatment through randomised trials, through sometimes observational evidence, through different forms of evidence, we can say, you know, we have here a scenario where a person declines in quality of life and then abruptly passes away. In the second scenario, the decline happens less slowly, and they levelled off and live for additional years.

So we can say the difference between those two scenarios is what health economics would call two QALYs gained with treatment, and then we would be interested in, you know, what have we paid for those two QALYs, and is it within what we would consider good value.

Next slide, please {XE7/8/8}.

So, as I say, it all comes down to saying when we compare the treatment state of the world with the

comparator state of the world, what have we done with cost, what have we done with QALY, what is the -- so, like I say here, we are interested in the relationship between the cost and the benefit of treatment and we measure that in terms of the cost per QALY gained. So the ratio of cost to QALYs, this tells us, you know, how much -- effectively what is one more year -- how much are we paying for one more year of perfect health. Again, as Mr Hawkins pointed out, that can be a small gain across a lot of patients, it can be a very large gain to one patient, health economics treats those the same. You can aggregate.

Again, this is one of the big differences in health economics compared to some of the other branches of cost benefit that we say that we allow interpersonal comparison and that I can take your outcomes and add them to your outcomes and we can discuss that in an aggregated way in a way that perhaps conventional cost benefit would not permit or would not appreciate.

Then at the end of the day the lower the cost per QALY gained, the greater the value of this treatment in terms of cost per QALY gained.

Next slide, please {XE7/8/9}.

When we think about that comparison and when we think about that incremental comparison, if we put the

comparator at the centre of this plane, cost effectiveness plane we call it, relative to a comparator, we have four potential states of the world.

Starting from the lower right, we can have something that is less costly and more effective in terms of QALY gained, so that is the win-win state. Conversely in the top left, we have a treatment that is more costly and less effective than the comparator, that is the lose-lose state. So it is quite clear we do not like -- we love the ones in the lower right, we hate the ones in the top left.

In terms of thinking about disinvestment of ineffective treatments, the south-west quadrant is of interest, but most of the action in health economics, as you can imagine, happens in this north-east quadrant. That it is more costly yet -- and more effective.

So next slide, please {XE7/8/10}.

The question then in this north-east quadrant becomes what is the relationship between cost and QALYs gained. So effectively we want to measure the slope of this line that is connecting the two points. If the slope of that line is less than 20,000 we are quite happy with it, if it is greater than 20,000, we have a discussion.

So in a very simplified way this is where most of the action in health economics happens.

THE PRESIDENT: You may be coming to the 20,000, but you heard what Mr Hawkins said about it. Do you agree that it is a figure of nebulous historical sources?

A. I would absolutely agree with that. People have been trying to track down the roots of 20,000 for a long time and people have theories, but I have never heard a definitive answer.

THE PRESIDENT: Fair enough, but what one draws from that is it is not a figure that can be improved upon in the sense that we are trying to assign a value to something that is essentially non-monetisable?

A. People are approaching it -- so I believe Mr Hawkins mentioned the opportunity cost perspective on the threshold. I think in that context that is monetisable. The other perspective, which I would say I am probably more an adherent to, is that this is the societal willingness to pay for health, that, as a society we have decided we value healthcare and we value improved health outcomes and this is what we are willing to pay for it.

So I take a more societal preference point of view, others take a more technical -- yes, a more technical, more quantitative approach to that problem.

THE PRESIDENT: But in each case how, without being subjective, do you map a non-monetary benefit -- health -- to a financial figure, whether you are operating at the individual quantitative level or the societal level?

A. Which is the ultimate philosophical question in health economics.

You can ask people a thought experiment: if I could add a year of perfect health to your life for £1 would you accept that treatment and most people would say yes. If it takes a billion pounds to add a year of life, would you accept that as good then most people would say no. So we have established at least there is a range in which we can accept things are acceptable and not acceptable, and then the £20,000 question, if you want to call it that, is where is the point that between those two extremes we can all agree on as a society.

THE PRESIDENT: Well, is it actually as simple as that, because you have left out of account ability to pay. You have included willingness to pay, but if you were Elon Musk and asked that question, then the answer might be very different to if you asked me the question because Elon Musk has several billions to buy Twitter with and he probably has a billion to spend on an extra year of life whereas I do not, so how do you factor in

your assessment, not willingness to pay, because we may all be willing to pay a billion, but we simply cannot.

A. This is how health economics tries to sidestep that individual willingness and ability to pay and say: this is societal willingness to pay. We all live in a society, we live in a society that has a single payer healthcare system and we need to make hard choices about how much to spend on our single-payer healthcare system versus other things that we would like the government to fund.

THE PRESIDENT: Fair enough. So the question translates away from Elon Musk and away from me to a societal question, but that means the ability to pay recedes because our society is able to pay large amounts of money on certain things, but it does not have infinite resource, so that simply sharpens the question of how do you defend the monetary value that you assign to a, let us assume, certain clinical health benefit?

I mean, are you not -- I am suggesting to you -- just plucking a figure from the air which is why the 20,000 is what we have got, even though no one actually knows where it came from?

A. I think that is a fair statement, yes. It is a rule of thumb, perhaps, that has solidified over time but is hard to say there is a clear justification or clear

reason why it is 20,000 and not 25,000 or not 15,000, yes.

THE PRESIDENT: Indeed, but even rule of thumb is giving it a certain accuracy which is entirely, can I suggest, spurious.

A. I think there is a normative quality to it that has come over time, but you are right, I absolutely agree that it would be difficult to pin down exactly why this number exists, and I think that is what some of the efforts to take a more opportunity cost approach to the problem are perhaps trying to resolve and giving it a strong basis for why it is exactly this number and not that number.

THE PRESIDENT: Thank you.

PROFESSOR WATERSON: But surely with opportunity cost, also it depends very much on what the opportunity for a particular individual is?

A. Yes, exactly, so it is not strictly a marginal cost in the way economists might normally try and think of it, it is the average cost at the margin, you know, on average how much does it cost the NHS to produce a QALY and can we make sure that we are not spending more on generating a QALY here than we could have used to generate over there. Because yes, the ultimate goal of all of health economics and of NICE is to maximise health within society, and you do that by -- by

promoting efficiency.

PROFESSOR WATERSON: But to come back to your earlier point about how you aggregate across people, this is a rather morbid example, but there are roughly 30 people in this room, so there could be two alternatives: one is that we know for certain that one person will get shot and killed, or we have a 1 in 30 chance that any one of us would be shot and killed, and you are saying those are the same thing, really.

A. Yes, yes, I am literally saying that, yes.

PROFESSOR WATERSON: Thank you.

A. Or at the very least, we would be indifferent to adding one 30th of a life year to everyone's life or adding one year to a single person, yes.

PROFESSOR WATERSON: Yes.

A. Next slide, please {XE7/8/11}.

So I have laid out the general principles of health economics and now where does NICE fit into this framework.

So NICE is the UK's health technology assessor, I think Mr Hawkins mentioned that its mission is to ensure that NHS resources are used as efficiently as possible, so again, this is the idea of maximising health within the available budget.

This includes dynamic efficiency as well as static,

so static says we want to do the most we can with the money we have available today, but dynamic efficiency says we want to make sure that we are spending the money in the way that does not only benefit us today, but it also maximises our advantage in the future.

So to achieve this mission, they have defined technologies with a cost per QALY gained in the range of £20,000 to £30,000 as typically a good use of NHS resources. In practice, this range might be even higher and Mr Hawkins touched on this as well, that it is not the single determinate of NICE decisions. An econometric study in 2015 showed that even at £40,000 per QALY there was only 50% chance of rejection.

So this is NICE's assessor role, and NICE is also a methodological leader, so its guidance around how to conduct these sorts of evaluations, how to conduct the modelling in these situations, has been adopted by a number of countries and HTA bodies around the world and has become the de facto standard for how to approach these sorts of problems.

There is a nice quote from Smith in BMJ saying:

"NICE may prove to be one of Britain's greatest cultural exports along with Shakespeare, Newtonian physics, the Beatles, Harry Potter and the Teletubbies."

I come from Canada and particularly Canada has

adopted almost verbatim the NICE guidance on how to conduct these sorts of evaluations, a similar situation in Australia. So there is quite a few countries that are basically modelled on how NICE approaches this problem.

Next slide, please {XE7/8/12}.

Within NICE, and again I may skim this very quickly, because Mr Hawkins probably did a clear view on this, the guideline programme develops treatment recommendations based on clinical and economic evidence. This programme routinely conducts economic assessments of older medicines. The technology assessment programme is perhaps more stringent. It assesses the value of a technology relative to one or more comparators, typically focusing on the newest and therefore the most costly technologies.

I make the point, though, in my position paper that there is nothing in NICE guidance or methods that would forbid or prevent the assessment of older technologies, and, indeed, the comparator in many technology assessments will be in older medicine or even a generic. So there is nothing preventing the inclusion of a generic per se in a technology assessment.

So although their purposes are slightly different, and in terms of purpose I should probably say how the

evidence is interpreted are slightly different, but the underlying methods that produce those estimates, particularly cost per QALY gained, are virtually identical, and indeed, the guidelines methodology references the TA assessment methodology. So they really do cross-fertilise each other, and I see no material difference in how you would approach an assessment for a guideline versus an assessment for a TA.

Next slide, please {XE7/8/13}.

So given that background and that framework, I will briefly go through my approach.

Next slide, please {XE7/8/14}.

In a stylised way, this is the general approach you would take to any sort of economic evaluation. You would review the literature to identify comparators, and in my case appropriate to 2012 with the assistance of an external firm who specialises in network meta analysis we conducted a literature review and conducted a network meta analysis, NMA is not my area of expertise.

Alongside that effectiveness evidence we looked at costs, so we took representative daily cost from the 2012 prescribing costs analysis data provided by the NHS, we combined those within the framework of an economic model, and I generated base case results and

then conducted probabilistic and scenario analysis in response to Professor McGuire's comments on my original analysis.

PROFESSOR WATERSON: Can I check: 2012 is a fairly crucial date. Do you know at what time of year 2012 this was done?

A. Yes, we took them from the October 2012 prescribing cost analysis data. This was the first time we saw the 67.50 per pack cost for phenytoin sodium 84-capsule pack.

PROFESSOR WATERSON: Thank you.

A. Next slide, please {XE7/8/15}.

As Mr Hawkins again has pointed out, there are data gaps around phenytoin owing largely to its age and the fact that it pre-dated systematic clinical trials. That data gap to me presented four options. I could either accept the data gap as insurmountable and essentially abandon the analysis and say there is no way to estimate the cost of phenytoin. I did not think that was constructive or useful for the purposes of this hearing.

Second, rely on clinical expert opinion to estimate the effectiveness of phenytoin. To some extent, we did that in the sense of understanding that this drug is still recommended, still seen as an effective, if third-line option for epilepsy. The concern here was that clinical opinion would not be able to estimate it

to the degree of precision we would need to do a quantitative analysis.

The third option was to adopt NICE's assumption, and again here, I must be clear that this is in the complete seizure-freedom category, to adopt NICE's assumption that phenytoin was no more effective than placebo with respect to complete seizure-freedom, or apply my own assumption, extrapolating from what we already knew about the efficacy of phenytoin in a first-line setting.

So if we can go to the next slide {XE7/8/16}.

That leads me to my proportionality assumption. As Mr Hawkins rightly points out, this is the fundamental point of any, I think, disagreement between me and the other experts.

So I made the assumption that given the similarity of oxcarbazepine and phenytoin in terms of their effectiveness in terms of first-line treatment, I understood no clinical reason to think that that relationship should not hold in a subsequent line of therapy. There was another study that I cited in my position paper that showed that as well, that there is a somewhat predictable decline in efficacy between lines of therapy.

So if I took the same relative decline in efficacy that was observed with oxcarbazepine and applied that to

what I observed -- to what Bill observed in 1997, I arrive at this 6.85 estimate of effectiveness. This works in the other direction as well. If I say 58% is 98% of 59.3, so this relationship holds in either direction, if I said what is 98% of 7.0% in the adjunct setting then it is the same, 6.85.

Next slide, please {XE7/8/17}.

I also made an equivalence assumption, so comparing the Bill and the Barcs study. So Bill is the first-line study, Barcs is the adjuvant study of oxcarbazepine. They did not test the exact same dose in these two trial, so Bill tested an average dose of 1,028mg, Barcs tested a defined dose -- had three dosage arms, 600, 1,200 and 2,400mg per day.

Given the 2,400mg arm was also the most efficacious arm of the trial, I felt that there was potential here to bias the outcome in a positive direction, so I excluded that, the highest dose arm, and combined the two lower dose arms to arrive at an average of 900mg which I felt was sufficiently close to 1,028 to make a reasonable comparison at a particular dosage.

The third slide, please {XE7/8/18}. Sorry, next slide.

Then finally moving from the five state to the three state to the two state model.

So probably we should read this from right to left. Again, as Mr Hawkins pointed out, I have two health states in my model. As I said, because the Bill study did not include -- did not -- only reported complete seizure-freedom, it did not report partial seizure-freedom, so I dealt with that by combining no response and partial response, which in turn NICE itself had combined a couple of health states from the cenobamate model which they used as a guide, I think, in developing their model for the guidelines.

So to me this is a somewhat logical extension of the same principle, but let us focus on the most relevant health state and the most rigorous evidence that is available for a particular health state.

As Mr Hawkins pointed out, this, I think, takes a conservative view of the value of phenytoin. I do not disagree with him at all. I have probably left value out of the model by ignoring that there is value even to a partial response, but I have focused on what I understand from Professors Walker and Sander is the critical outcome in this field and where I felt the evidence was the strongest.

Next slide, please {XE7/8/19}.

MR O'DONOGHUE: Sir, I see the time. Would it be a convenient moment for the shorthand writer?

THE PRESIDENT: Well, Mr O'Donoghue, thank you for the reminder.

We take breaks, Dr Skedgel, to enable fingers to be rested. If that is a convenient moment for you, we will rise for ten minutes, and resume then. So thank you very much.

(11.40 am)

(A short break)

(11.54 am)

THE PRESIDENT: Dr Skedgel, welcome back.

A. Next slide, please {XE7/8/20}.

So these are the results from our network meta analysis. The dotted line across the middle represents phenytoin and everything is presented relative to the efficacy of phenytoin.

You can see oxcarbazepine is the only one that is significantly better than phenytoin. It is a first-line treatment and technically should not be a comparator to phenytoin in the adjunct, it is only there as the link in my proportionality assumption.

Most of the others are less effective in terms of their expected outcome but not statistically significant at a 95% level with the exception of placebo and Zonisamide at the far right.

Next slide, please {XE7/8/21}.

That is the effectiveness -- efficacy side of my analysis, and then I combine that with the cost analysis side which says for a representative daily dose most of these products have a very specific dose, a couple of them report a range or pregabalin in particular, three-quarters down the list, has a -- it seems you can use 150 or 300 at physician judgment, so we took the mid-point of that to say this is the representative daily dose, for purposes of costing.

Next slide, please {XE7/8/22}.

When you combine those estimates of efficacy and calculate that through to say, well what is the implication of this efficacy in terms of QALYs gained or QALYs experienced under each of these treatments, we can plot the lifetime expected QALY of each of those against their lifetime expected cost.

By economic principles/convention you take the lowest cost, compare the lowest cost alternative as your comparator and say: all right, from here, as we add cost, what are we doing in terms of QALY outcomes.

So anything to the right of that pregabalin comparator point is more efficacious, and anything above that pregabalin comparator point is more expensive.

THE PRESIDENT: Now, Dr Skedgel, you are in this graph talking at a statistical level, not at an individual

level; that is right, is it not?

A. Yes, this is -- yes, a representative outcome for each of these treatments.

THE PRESIDENT: Indeed. What, then, do you do with the fact that phenytoin -- the drug we are interested in -- is prescribed by doctors in a targeted way -- let me unpack what I mean by that and you can help me on whether it makes a difference. So we have heard very helpful expert medical evidence on how phenytoin is used, and we know it is a third-line form of treatment that is used in cases where lines 1 and/or 2 are insufficiently effective to achieve the gold standard of no seizures, and at that point you start playing with other drugs to add to the cocktail mix, and using medical judgment and patient choice you will hit upon phenytoin, which may or may not be effective, and you would only stay on it if it is effective.

Now, that is a summary which I am sure can be corrected in closing, but why do you not take that as my understanding of how it all works, but my point is that you are not looking at the universe of epileptics. You are looking at a far narrower universe that is not in any way randomised or randomly selected. You are looking at a group of patients who have quite consciously been prescribed sodium phenytoin because,

assuming they continue to be prescribed it, because it is in a clinical judgment efficacious.

Now, is that not the very reverse of a statistical approach in that what we have is we have a case where if the drug is being prescribed on a continuous basis, there is, not in a randomised way but in a very concrete, specific way, a professional evaluation that the drug is efficacious, and my question -- it has been a long time coming -- my question is this: should we not be looking at the clinical judgment and the patient improvement at the individual level given that that is what is going on in the real world, rather than a graphical representation as to efficacy in a generalised sense comparing phenytoin to other drugs given that we know that some drugs work with some patients and other drugs work with others, and you do not just throw the same batch of drugs at the same bunch of people and get varying outcomes, you apply judgment.

A. Yes, I think your question comes back to the point we discussed a little while ago about health economics' approach of aggregation.

We are indifferent whether it works for one patient and does not work for 99 patients or that each patient gets one 100th of a benefit. So by that logic, we are interested in the average expected outcome, not the: it

worked for this person but not for that person. If we had a terribly-sized, terribly-powered clinical trial of two people, and it worked for one person and did not work for the other person, in the most simple world we would say: on average there is a 50% benefit with this product. So we would not get down to the individual level.

Mr Hawkins raised the point about patient sub-groups and patient heterogeneity. So yes, absolutely, sometimes, in some models, you would say: this group of patients -- and I think we heard during the clinical testimony that Han Chinese probably should not use phenytoin, that there is a particular risk of this phenotype. So you could get down to that sub-group level and say: well, you know, at that sub-group, these people are likely to do much worse than this other sub-group.

But we have approached it, and consistent I think with what Mr Hawkins described at the aggregate level, and just said: we are interested in the expected outcome across the population using this drug.

THE PRESIDENT: Well, it may be you have put your finger on the problem because where all this is going to is the value of the drug and how that then interrelates with price, and I am not going to go there with you because

we are going to have to think about that ourselves, but when one is looking at price, cost and value, is not an aggregated value actually not very helpful because, to take the courtroom example that Professor Waterson used a moment ago, we might know that there is a 1 in 30 chance of something unpleasant happening to someone in the courtroom, and it might be the case that in other areas of clinical evaluation you have to take that sort of statistical approach, but that is precisely not what is going on when one is prescribing phenytoin because one has a clinical assessment that, if one is continuing to prescribe, there is this clinical benefit which is a removal of seizures from someone who previously on their line 1/line 2 treatment had them, and what that means, I am putting to you, or suggesting to you, is that the idea of looking at a universe of people is just not helpful because the very process of selecting patients and treatment is informed.

A. So you are suggesting not every patient is equally likely to get each of these comparators, there was something in their clinical history or in the judgment of their physician that meant they were only ever going to get this one, it was not an open competition.

THE PRESIDENT: That is exactly what I am suggesting. What I am saying is there is a process of application of mind

which I think we did get from our clinical experts, which indicates that you are not going to just throw any old drug at any old patient; you are going to apply an extremely sophisticated judgmental approach as to what you prescribe to which patient, and your Han Chinese example is one of those factors that will inform choice and there are a myriad of others which I am not going to go through because I need to re-read the evidence of the doctors, but the fact is that is what they have told us.

A. I absolutely understand the point, and you are right, any economic model -- I think frankly even any clinical trial is a somewhat stylised -- is somewhat stylised written evidence, because, you are right, not all of these alternatives may be equally probable for any individual patient.

The goal, however, is to come up with an average or a representative or an expected outcome kind of washing out some of those individual factors.

If we think: well, there is an individual factor why one person might be put on this drug and an individual factor why a different person is put on that drug, but if we run a clinical trial with enough people we would hope that those individual differences cancel each other out.

THE PRESIDENT: I quite understand why this sort of process

could have enormous value in, let us say -- let us move away from the clinical and into the road traffic. You might say: if I spend a few million pounds on re road-surfacing certain roads which are very slippery there will be a benefit in that the number of accidents on the road will be diminished, and that will be a benefit even though one cannot tell which particular cars will avoid the accident and which particular driver's lives will therefore be saved or avoiding a nasty accident, and we do not know, but nevertheless there is still a benefit, but here one is not approaching it at that statistical level. The way in which the benefit to the patient is being computed is by reference to that specific patient.

In other words, we have a fixed point which is the price that is paid by the NHS for this particular capsule, and we then have the value to that particular patient of that particular capsule which is not calibrated by reference to, well, there is a 1 in 100 chance it will be better. It is not done that way, it is done on the basis that: we have gone through the line 1/line 2 drugs, we are trying a variant on the cocktail, and using our judgment we think that for this patient, this drug will avoid that seizure.

Does that not mean that when one is trying to

articulate value to price you need to look at it through the lens of why it is that a doctor is prescribing it because, frankly, if you gave me phenytoin, I am not an epileptic, the price to value ratio would be nil. It would be a pointless expenditure.

Now, that may be true of a large number of epileptics who can be treated through line 1/line 2 treatments and what we have is a small and diminishing number of patients who, according to clinical judgment, are being rendered seizure-free -- we can talk probabilities, but we will not -- are being rendered seizure-free through the administration of this specific drug to that specific patient in that specific doctor's judgment.

So what I am really asking is what do we get out of a statistical analysis when we are selecting the patients to whom the -- in relation to whom the cost is incurred?

A. I do see your point about there being -- we might want to call it selection bias, there are particular reasons why particular patients would be put on one product compared to the other product. I do not think I have a good answer for you in saying that health economics can deal with that. We are capable of dealing with patient heterogeneity in the sense that we have talked

about but not that sort of individual decision-making factor.

We are constrained having to work with expected values, but I think maybe the only thing I can say in support of that approach is that it follows from the double blinded approach of a clinical trial. Within a clinical trial you are not being assigned on the basis of the physician's judgment, they are being assigned on the basis of a randomisation algorithm, and, you are right, by that randomisation algorithm you may not have ended up on the single individual thing that would have worked best for your genetic profile, and so we are taking that, you are right, somewhat -- an approach that is useful that has limitations in some contexts and expanding on that and building on that in our approach.

THE PRESIDENT: Dr Skedgel, please do not get me wrong, I am not trying to undermine the entirety of health economics in this country, far from it. I am accepting that your approach to assessing value and benefit in the general term is hugely important and beneficial. Please do take that as read.

What I am saying is that, and putting to you, is that in the context of the enquiry that this Tribunal is being required to undertake, which is is the price too far above the cost to be defensible in competition law

terms, one question that we are likely to be asking ourselves is what value does one get out of the dispensation of this particular drug, and if one did not have a targeted prescription to a particular patient, then of course, large numbers might come to assist and my road traffic case is a case in point. If we were trying to say: is one spending too much by spending £10 million on a road improvement while the benefit one gets is a 10% reduction in accidents which means ten fewer deaths a year, well you then have a comparator and it does not matter which drivers we are talking about.

My point is that here when one is trying to say: is this price defensible over that cost, both of which, let us assume, we know, the value is not derived in the context of this particular case by reference to any kind of randomised, double blind or not, statistical analysis, it is informed by clinical choice which is quite deliberately skewed towards only prescribing if it is actually benefiting the patient.

So the value is moving in the context of this enquiry from the statistical to the very individual, because there is a correlation between prescription and benefit and, therefore, value.

A. I think that raises two thoughts with me.

I think it is important to make it clear I am

approaching this valuation for new patients, so I have overlooked the value to I think what you have been calling legacy patients, so this is starting from a stylised point of equipoise. We are starting from a point where every drug is equally likely to be prescribed for any particular representative patient and in that state of equipoise what is the value of these different products.

I think the second point -- and I am not 100% sure how to process this one, but I think the problem you are describing probably applies any time there is more than one treatment available for a particular indication, that there will always be some judgment involved in why I have given you ibuprofen instead of paracetamol.

THE PRESIDENT: I would accept that, but I think in many cases, the enquiry in terms of spend operates at the aggregate level as well, and so what you will be saying is if I am spending 10 billion on drugs what, across the patient population, is the benefit, and there I quite understand that one would be driven to this sort of analysis.

My point, I think, is -- and I think you are accepting it, but do tell me if you are not -- that given the enquiry that we are here undertaking, which is price of a particular product versus cost of

a particular product and can the gap be justified by inter alia value, we are not looking, because we do not have to and because that is not how it works, on the facts of this case. We are looking at the specific patient because we can reliably take into consideration that doctors, generally speaking, are competent, generally speaking are conscientious and so generally speaking will prescribe phenytoin either to a new patient or to a legacy patient where it is clinically justified.

It is that individuality that I am wondering whether it does not undermine, because I am accepting everything you are doing here on a statistical level, but whether it means that that approach is less apposite in the context of this trial than it might be in the context of the myriad of other questions that one could ask in the context of health economics.

A. Yes, I think that is a fair point. I think that is a fair point that at any individual product level there will be particular reasons why you may or may not use this one other than simply its cost and its expected benefit, yes.

THE PRESIDENT: Thank you very much. I am sorry that took a long time. I am very grateful to you.

PROFESSOR WATERSON: Could I raise a different point just to

check my understanding.

I think you started out by saying that because of the nature of this graph, you would prefer products to be in the bottom left quadrant rather than the top right quadrant.

A. Relative to the pregabalin, yes.

PROFESSOR WATERSON: So that makes it somewhat difficult to rank the products in the top right because phenytoin happens, in this case, to be up at the top, but that does not mean it is necessarily better than one of the others because what you would ideally like would be for it to be lower than the less -- than the -- in terms of lifetime costs than -- as well as being more efficacious?

A. Exactly, the assessment changes. So if we are in that south-east quadrant, you are right, we can unambiguously say better, this is better, it is less expensive, and it has a better outcome. It is unambiguous.

In this quadrant, it is ambiguous and we begin talking about relative value.

PROFESSOR WATERSON: Yes. It is just I initially got confused because I like to think of indifference curves and so on as an economist, and of course this is not the normal quadrant for looking at indifference curves.

A. Yes, yes. Well, actually, that is probably a good segue

into the next slide {XE7/8/23}.

We have plotted everything relative to pregabalin, and then we apply the threshold. So the threshold is saying: relative to our comparator, do we believe this particular point on our cost effectiveness plane represents good value or not. So we can draw a line with a slope of £20,000 per QALY gained and say what is above that line and what is below that line is a way of distinguishing what we think is good value relative to pregabalin.

What I find is that phenytoin is very close to the threshold, but it is the only one that is slightly below the threshold. So that is the basis of my conclusion that at its expected value, phenytoin would appear to meet NICE's £20,000 threshold.

PROFESSOR WATERSON: Right.

A. If we go to the next slide where I can put that conclusion into context, the reality is, yes, you know, there is a lot of similarity in all of these products in terms of their cost and their outcome. We are looking at the marginal effect -- the marginal cost and the marginal benefit relative to the previous comparator, but, yes, any reasonable person would look at that and say there is very, very much a similarity between these products.

PROFESSOR WATERSON: Yes, and so are there products within the range of treatments for epilepsy which would be way different from this line, either way below or way above or do you not happen to know?

A. I would not be able to comment on individual drugs, but I do observe in the table that Mr Hawkins presented earlier today that he found relatively small changes in cost and outcome as well which reassures me that we are not -- that we have not somehow landed on a different order of magnitude around any of these things, but, yes, I cannot say that there is a particular product that would be miles away from this collection of points.

PROFESSOR WATERSON: Thank you.

A. Next slide, please {XE7/8/25}.

Now that we sort of understand how economics thinks about value and how NICE approaches that value assessment, I think it is useful to have a very quick discussion of NICE's role in price setting. So again, Mr Hawkins has been clear that NICE does not have a formal role in setting any prices, but in my opinion, in my expert opinion, I believe they exert a strong indirect influence on prices.

So manufacturers see a positive NICE recommendation as critical to market access and meeting that threshold is, in turn, critical to a positive recommendation. So

manufacturers account for the threshold in setting their prices. In a previous consulting life, I was primarily a modeler for a different consultancy, and in my time there built a number of what we called economically justifiable price models: so let us work backwards from what we think the expected QALY gain is to arrive at a price that is near but not above that threshold, and that will be the starting point of our negotiation around price. So in that sense, that is the sense that I see NICE exerting indirect influence on prices.

In context where a TA, after the expert review group perhaps applies some of their assumptions or updates some of the original assumptions in the model, quite often you will end up on the wrong side of that threshold now, and NICE may request what they call a patient access scheme which is fancy wording for a price discount, to bring that cost below the acceptable threshold. So, again, in that sense, NICE is beginning to exert a slightly more direct influence on prices.

Likewise, even in a guideline, NICE can indicate a price that they think would be acceptable value for money. I pull out this quote from the 2012 epilepsy guidelines that says -- I am sorry, I absolutely cannot pronounce that word, but it should be offered as

a treatment provided that the acquisition cost falls by at least 50% from the price in June 2011. So to me that is a pretty clear example of NICE exerting an influence on prices.

Next slide, please {XE7/8/26}. So there has been much discussion about the uncertainty around this, and my original analysis focused on the base case, the expected values from all of this analysis and at Professor McGuire's suggestion I added in scenario analysis and probabilistic analysis.

Next slide, please {XE7/8/27}.

As Mr Hawkins pointed out, it is very true that my assumptions around the efficacy of phenytoin is the key driver of the outcomes in my model. So, as part of an overarching scenario analysis I wanted to test how far away can I get from my assumption in the model and still be within the upper range of what NICE might consider cost effective. So I found that at an efficacy as low as 2.9% compared to my base case of 6.85%, phenytoin would still meet that £30,000 threshold. That is a 50% relative reduction and to me indicates there is some robustness in my results to that core assumption.

Next slide, please {XE7/8/28}.

Likewise, I tested some of the other key prices at the suggestion of counsel. You can see the price I have

tested is the high end. Any of the prices that seem to have come after that pricing question lead to a more favourable cost per QALY gained.

Next slide, please {XE7/8/29}.

Before I get into my probabilistic results I think it is useful to draw a distinction between what a deterministic analysis and what a probabilistic analysis is. So if we wanted to understand the body mass index of everyone in the courtroom today we would say -- we would measure everyone's height, we would secretly measure everyone's weight, and we would calculate an expected BMI, and that would be our representative BMI for the room, that would be our best estimate of any individual in the room.

If we want to understand, yes, there is -- there is variability around the height of people in the room, around the weight of people in the room, so if we wanted to account for that and understand we have our expected, but how much range is there around the individual numbers.

So if we go to the next slide {XE7/8/30}, this is where probabilistic analysis comes into an economic evaluation. So to understand the range around that expected value, we can assign a probability distribution to the parameters. In our simple example we are

interested in people's height and their weight, so we can say: well, everyone is -- there is some minimum height, we will apply sort of a right skewed probability distribution to that problem and we will draw from that sample and estimate the range of people's heights that might come out of a probability distribution, and we will do the same thing for weight, and we would expect those numbers to converge on the mean of those probability distributions.

That said, there is no requirement that it must reproduce to the decimal place what that mean estimate was, we are just expecting it will tend towards the central estimate of any probability distribution.

So if we go to the next slide {XE7/8/31}, we can draw N samples. So typically in health economics that is usually somewhere between 5,000 and 10,000. Partly it depends on how complex the model is and how long it takes to run these probabilistic scenarios. I can say health economics is a pragmatic discipline and even analyst time is a scarce resource and so there is a limit to how much time you want to spend running a probabilistic analysis.

So we would generate a series of probabilistic iterations, drawing randomly and just paring these things up. What is the value we have drawn for height,

what is the value we have drawn from weight and what does that imply for the BMI and just repeating that process 5,000, 10,000, sometimes 20,000 times, and that should get us a mean across those probabilistic iterations that is relatively close to our expected -- to the expected BMI that we measured -- that we calculated just by calculating an average for everyone in the room.

So if we go to the next slide {XE7/8/32}, this is what my probabilistic analysis looks like across the different comparators in my model. So we see a cloud of points. The shape is relatively typical for a probabilistic analysis. As outcomes go up, costs also go up. We have this sort of upwards sloping cloud of points.

On just pure visual inspection I see nothing to indicate that phenytoin is uniquely uncertain or has a different uncertainty structure than the other comparators in my model.

If I move to the next slide {XE7/8/33}, this is a zooming in on phenytoin in particular. The dot shows my expected value based on the base case analysis, and the cross shows the mean of the probabilistic analyses. There has been some controversy about whether that difference is consequential or not, and I think that is

a matter of expert opinion. I am not -- the challenge in any of these probabilistic analyses, particularly in a NICE context, is we have a clear decision rule for what represents money for -- good value for money in the base case, in the deterministic analysis, but there is no sense of how much uncertainty is too much uncertainty for decision-making purposes.

So, again, I think this will be a point of contention between perhaps me and Professor McGuire of what the -- how consequential that difference is.

If we move to the next slide {XE7/8/34}, this is slightly re-arranging the cost per QALY decision rule. The ICER says what is the ratio of cost over effect, and is it less than our willingness to pay for a QALY. We can re-arrange that, without changing the information that it is providing, we can re-arrange it and produce that same information in a different form. The problem with the ratio is if any of those numbers are zero, the ratio falls apart, you do not have a nice continuous function.

Re-arranging it lets you come up with a nice linear continuous function that you can plot in this sort of a way. So this is from my probabilistic analysis. This is saying what is the net monetary benefit, re-arranging that ICER calculation to think about net monetary

benefit. What is the gain in effect, here meaning QALYs, less the change in cost, and so exactly as Mr Hawkins pointed out yesterday or today, we want to understand is that number -- is the thing we value in monetary terms greater than or less than the cost that we are paying for it.

So what I find is, again, phenytoin in orange here very close to that zero threshold where you are saying there is positive value relative to pregabalin, whereas the others are below that line of positive value.

It is true that in my probabilistic analysis that net monetary benefit is slightly negative, whereas -- slightly negative implying an ICER from the probabilistic analysis that is just beyond 20,000 compared to my baseline which is just below 20,000.

Next slide, please {XE7/8/35}. This is where the -- quite a well-known, well-respected health economics author has called it "the irrelevance of inference". If we go to the next slide {XE7/8/36}. Health economics is not a 95% confidence discipline, it is a decision-making discipline. So on that basis, we recommend an expected value decision rule that does not necessarily take into account uncertainty.

Taking this approach has been shown to maximise the portfolio -- the value of a portfolio of decisions, and

under this approach uncertainty is irrelevant to the decision and is only relevant to making a decision about whether it is worth investing in further research that could reduce that uncertainty.

So if we go to the next slide, I will try to visually present why we are taking this decision-making approach rather than a statistical inference approach {XE7/8/37}.

So if this was the choice in outcomes faced by a physician or by a patient, it is relatively clear most people would prefer the blue distribution to the right. If this is QALYs gained with particular treatment, most people would say I prefer the blue treatment to the red treatment.

If we move to the next slide {XE7/8/38}, if we start compressing those distributions, maybe this is, maybe this is not, maybe there is or is not some 95% statistical significance between these two, but most people would still say: I would prefer the blue treatment to the red treatment.

If we move to the last slide {XE7/8/39}, even in this scenario, where there is very clearly no 95% confidence between these two, most people would still say: I will take my chances on the blue treatment compared to the red treatment, all other things equal of

course. So that is the justification for why inference is not a useful method of decision-making in this context.

The point Claxton makes is that making a decision on the basis of 95% confidence which would say: well, we cannot reject that red is in fact better than blue, imposes a cost because we would -- in most cases we would expect that blue is going to be better than red, and that decision on the basis of statistical inference rather than expected value imposes a cost, an opportunity cost in terms of potential health gains.

Next slide, please {XE7/8/40}.

So that is my teach-in, that is my analysis.

One final slide here {XE7/8/41}. So at a minimum, if we think to that zoomed-out version of my scatter plot, phenytoin looks very similar in terms of value to its adjunct comparators and beyond that I find it would probably have met NICE's £20,000 threshold.

I am confident that the model and the results are robust and that the assumptions I made to overcome that particular evidence gap around the efficacy of phenytoin is reasonable.

More so, I am personally convinced that drawing from the clinical experience of phenytoin in that first line trial is probably a more plausible assumption in my mind

than the very conservative assumption that in the absence of evidence that it is more equally effective let us assume -- or sorry more effective than placebo, let us assume that it is no more effective than placebo.

Thank you. That is my presentation.

THE PRESIDENT: Dr Skedgel, thank you very much. We are very grateful to you. We will see you again shortly when you will be cross-examined. Thank you.

MS MORRISON: Professor McGuire, if I could just call him forward.

Just while Professor McGuire is getting settled, I do not know if anyone again would find hard copies of the presentation useful to have.

THE PRESIDENT: Yes, indeed, thank you.

PROFESSOR ALASTAIR MCGUIRE (affirmed)

THE PRESIDENT: Professor McGuire, welcome, do sit down, make yourself comfortable. You should have some water there, and a glass, and I hope you have your presentation that you are going to be taking us through, but first there will be the formalities of introducing your reports into the record.

Examination-in-chief by MS MORRISON

MS MORRISON: I am hoping this time that you will have your first report or your report in front of you already in hard copy. For the Opus reference it is {XE3/3}. If we

could go forward to page {XE3/3/29} of your report, Professor McGuire, and bring up page {XE3/3/29}, can you just confirm that that is your signature when you get there?

A. Yes.

Q. Can you confirm that the opinions expressed in your report represent your true and complete professional opinions on the matters to which they relate?

A. Yes.

MS MORRISON: The presentation should appear on the Opus screen now.

Teach-in by PROFESSOR MCGUIRE

PROFESSOR MCGUIRE: Okay, could I have the first slide, please {XE7/7/1}.

I am developing a cold so I am going to apologise once for my coughing and sneezing.

THE PRESIDENT: No apology needed, Professor.

A. Okay, right, thanks.

I am Alastair McGuire, I am an economist by training and professor of health economics at the London School of Economics in the Department of Health Policy. I suppose partly in terms of my relevance to this case I have sat on NICE guidelines committees for type 2 diabetes, twice in fact.

Next slide, please {XE7/7/2}.

I want to go to the objectives of my presentation in a way. I have got kind of two parts. I will say very little about the detail for Dr Skedgel's modelling because you have been through that quite concisely with both James Hawkins and Dr Skedgel himself.

I think my main focus really wants to answer some of your questions about this aggregation problem and who chooses the choice set and how that feeds into the NICE appraisal process and to the pricing agreements.

I will probably go through that after the second slide or I will come back to those points in aggregate after the second slide, two slides in, rather, from here, and I also want to relate the NICE process to the pricing regulations that exist within the NHS and then get on to whether a QALY analysis reveals anything about economic value of a product.

So next slide, please {XE7/7/3}. I should be able to get through some of these quite quickly because both Dr Skedgel and James Hawkins have introduced you to the notion of a QALY. Here is this four-quadrant diagram again that Dr Skedgel had. It is cross-wired at this comparator point, so you have got the comparator. NICE has this comparator well-defined as a reference case. The reference case is essentially what the standard therapy is at this point in time but as was pointed out

by a couple of the witnesses, or in the teach-in, it could be a do nothing, there might not exist anything.

The axes are the incremental treatment costs and it is the treatment costs, so these treatment costs include the price of a new therapy, a new drug, for example, but they would also include the treatment costs associated with treating side effects from the therapy and also any treatment savings that are netted out from this treatment cost.

Then on the X axis is the new treatment which is under the NICE guidance methods really expected to be in terms of QALYs. I will come back to what QALYs are in a moment, but essentially I see them as a unit of health benefit gained from any treatment, and within this four quadrant diagram, you also have this £20,000 per QALY which is, as has been discussed, is a kind of threshold: it aids decision-making, it is not a black and white determination, it is an aid to decision-making. Where the £20,000 came from nobody really knows. Anecdotally, if you got Sir Mike Rawlins into a dark room and threatened to beat him up it is said that he would say the 20,000 in 1999, when NICE was set up, was the median earnings in the country, but that is anecdotal evidence, right.

There is now -- of course, it is an empirical

statement, and there is now an attempt to try to get some empirical worth put on this. There is work undertaken at the University of York which tries to look at across 26 disease areas whether the expenditure in these disease areas gives rise to what level of QALY essentially is attained.

All sorts of statistical problems with that, you have higher expenditure because you have lower life expectancy in some areas or not, but they have come up with a figure which is £15,000 per QALY, and that is actually used by the Department of Health to justify their impact analysis in this area, but NICE uses in its guidance, and I will come to the distinguishing features between guidance and HTAs which James pointed out, and its guidance it essentially uses this £20,000 per QALY. In the HTA process, which is for new drugs, and although Dr Skedgel said there is nothing methodologically to say that generics could not be put through an HTA programme, I know of no generic which has been put through an HTA programme, so it is really the HTA is for new drugs and I will come back to that as well.

The threshold for HTAs does change. It changes in a number of ways. It goes from £20,000 per QALY. If it is below that the new therapy would be accepted as compared to the comparator, and in that sense it is

a sort of opportunity cost element of what is the opportunity cost of displacing an existing treatment in the NHS, but it goes up to £20,000 to £30,000 per QALY if there are other arguments to come into play.

One of the other sets of arguments is about uncertainty, I will come back to that in the next slide, and then there are specific disease populations and severity of disease modifiers which drag the threshold right up to 100,000 and beyond for some very rare conditions.

THE PRESIDENT: I was just going to ask you about the point you made a moment ago of no generic having been put through an HTA programme.

A. Yes.

THE PRESIDENT: That is presumably because generics are substitutes, there is price competition, you have a price that will be essentially good value. There is no point particularly in running the expense of an HTA in that regard because you have something which is an established, inferentially old, medicine where it would be a waste of limited resources to do an HTA, or would that be something you would reject as an explanation?

A. No, you could say that, but I would also say compounding that that the prices have already been established for generics. That if generics are on the market, the

prices will have been established and, therefore, you are not using the HTA to see where the price might be through a threshold type of analysis, does it get up to £20,000 per QALY or not, but, yes, I would agree largely with your comment there.

Just at the bottom left of this slide there is the conversion of the incremental cost effectiveness ratio, that ratio of the new treatment, is it more costly over the new effect in terms of QALYs being less than £20,000 per QALY. Essentially, if you are in the north-east and the south-west quadrant of this diagram, you can get negative ratios, so they try to linearise it to try to get rid of that ambiguity, and, therefore, they make it equivalent to this incremental monetary benefit idea where the QALY difference is multiplied by the threshold, and you take -- net out the treatment costs.

Next -- before I say the next slide, should I say something about the costs as well? The treatment costs are based largely on list prices being incorporated within the treatment costs, and these list prices of course are agreed prices after the drug has been put on to the market, has market authorisation, and these list prices are quite important to the multinational companies who set them with the National Health Service.

The UK is only about 3% to 5% of the pharmaceutical

market globally, but other countries use the list prices in the UK to reference their drugs -- benchmark their drug prices in their own countries, especially in Southern Europe and Eastern Europe, and I think that is quite important because that means that once the lowest price is established it is then used as a benchmark elsewhere, but it also means that I think companies are more willing, let us say, to negotiate down from the list price and although it is just my opinion, I think that it is very common that these list prices are negotiated down within the NHS generally after they have gone through or during the process of going through some kind of evaluation which I will get to next.

Next slide, please {XE7/7/3}.

PROFESSOR WATERSON: What you were talking about then would relate to new therapies?

A. Absolutely, and that is the HTA process and that is largely what I am dwelling on here.

PROFESSOR WATERSON: Yes, understood.

A. So the HTA programme within NICE, as I have said, really only looks at new therapies. I know of no generic that has gone through an assessment in that process.

The generic assessment is part of what is called the clinical guidelines or the guidelines assessment which I will get to later on.

The second slide says that essentially NICE wants to know how conclusive the evidence is in terms of the ICER, the incremental cost effectiveness ratio, the ICER which has been calculated for any new therapy within the HTA process and to do that it undertakes an exercise that Dr Skedgel has done for phenytoin which essentially says: let us take some of the parameters out of this calculation, which is fairly mechanistic, take parameters out, give them a distribution and then take random draws from that distribution in a simulation where we will simulate what answer we get with this probability sensitivity analysis to see how sensitive the result to ICER is to changes in these parameter values.

That is what the slide at the bottom here shows, the red dot is essentially saying: this is a therapy that has been assessed, and its deterministic assessment, as Dr Skedgel defined it, the deterministic assessment, the one-off best case analysis, not taking any account of uncertainty, takes us to the line. Doing this simulation exercise then gives us a simulated sort of distribution of the expected value of the ICER, and the greater the uncertainty, the less likely NICE is willing to accept the new therapy at that £20,000 per QALY threshold. It may accept it between £20,000 and

£30,000, but it would routinely ask for more information, better clinical data, is it an innovative therapy, could you go to a specified at risk population and get a better ICER?

The second form of uncertainty which was touched on but I think is much more important and I will come back to that right at the end is structural uncertainty where NICE says: well, have you developed a model which you are very confident of in terms of its overall structure, and if you are not, if the types of assumptions that you have made to put into that model are not clear-cut and not well founded, change the model, change the structure of the model, and see what sort of outcomes you get, and I can come back to that. I just want to distinguish between the two at this point.

Now, as promised, I said I would get back to your choice in aggregation problem. I routinely nowadays tell my students that healthcare is about insurance. We have a social insurance pack in the National Health Service, and I routinely tell the clinicians in my class that they are actually in the insurance business. They are delivering the clinical treatment benefit off the insured, the social insurance, which comprises National Health Service.

Now, that then gets you into a whole discussion

which you started with Dr Skedgel about what it is that clinicians are doing and whether the evidence that they are working on in terms of averages actually relates to individual patients, and I think it is very muddied, but if you think about it as a social insurance package, then that social insurance package is trying to work out what is the package delivery that we are going to arrive at, and that is, I think, partly what the guidance -- NICE guidance assessment is all about, and I will come back to that as well.

I think in terms of the social insurance package, the NHS is interested in averages. It is interested in averages because it is trying to work out for at-risk populations what is the average effect of a treatment and what is the average cost.

If you multiply the average cost by the prevalence of the treatment, you get information on budget, and that budget is predetermined for the NHS by Parliament. So it is working within a budget-constrained social insurance package where it is trying to work out somehow what is the consistency between new therapies coming in in terms of not breaking that budget, which is predetermined, and in terms of what we can deliver to the population.

So that £20,000 per QALY element here is essentially

trying to say: well, that is the opportunity cost of one unit of health benefit, a QALY, as the NHS currently delivers it. If within a budget constrained package, then we are introducing new therapies, we are going to have to displace old therapies, okay.

Next slide, please --

MR DORAN: Sorry, just before you move on from that Professor McGuire, you say on the bottom of this on the left-hand side:

"HTA assessment not relevant to unbranded generic products."

So it is not valuable -- you say "not relevant", one does not reassess their role?

A. I know of no unbranded generic which has been through a NICE HTA assessment.

MR DORAN: I accept that, but not relevant, you say?

A. Well, if they have not been through that assessment, I do not see how it can be relevant to it.

MR DORAN: But not in a comparator?

A. Oh, yes, the generic could be the comparator.

MR DORAN: Yes, okay.

A. But you are not assessing the generic then, you are assessing the new therapy relative to the comparator.

MR DORAN: And you would not reassess the generic -- put it on the other way round and reassess the impact of the --

A. Not in an HTA, no. Not to my knowledge.
THE PRESIDENT: Two questions, one arising out of that. Suppose the generic increases in price a thousandfold.
A. That is why we are here, is it not?
THE PRESIDENT: Well, I agree. So why --
A. But NICE has not assessed it through an HTA. You would have to ask NICE why.
THE PRESIDENT: Okay. You see, I quite accept your statement that this has not been done, but not relevant in your slide implies it should not be done. My question --
A. When we go two, three slides on, that will explain why I think it is not relevant.
THE PRESIDENT: Okay, you can come back of course and answer that then.
Secondly, you mentioned a moment ago that the budget is predetermined by the NHS -- for the NHS by Parliament. Are you referring to an overall budget of the NHS or for the NHS, or are you referring to a specific budget that is hypothecated to pharmaceutical products?
A. The overall aggregate budget. So for each year a budget is set. That is £18 billion just now, for example.
THE PRESIDENT: For the NHS.
A. For the NHS.

THE PRESIDENT: So you cannot, by reference to parliamentary determination, state which part of that £18 billion is to be appropriated to the purchase of pharmaceutical products?

A. No, but as I said, this threshold which is only a guide, other things come into play -- uncertainty, needs of the population, wider social concerns, etc -- this threshold helps determine when a new drug is coming into the NHS whether it is consistent with lying within that budget by displacing another therapy at £20,000 per QALY.

THE PRESIDENT: I am grateful.

Final point: you quite rightly said we are here because the price of sodium phenytoin capsules is said to be and has been found to be by the CMA too high. Are you disagreeing with the points that I think I had reached with Dr Skedgel that when one is assessing not on an NHS global basis but by reference to the price for this particular generic, its cost, and the value that is derived, the weight that one attaches to value in terms of a justification for price is one that ought to be judged at the individual patient level rather than at the statistical aggregate level --

A. No.

THE PRESIDENT: -- or do you disagree?

A. I disagree with that, yes.

THE PRESIDENT: Would you mind explaining why?

A. Partly because it gets back to this social insurance idea. Now, I think it is very muddied, so I disagree maybe 80% and 20% I would agree, and I will tell you why it is muddied in a moment, but I think that within that social insurance contract that we have as citizens within the UK, we have allocated a budget somehow. I do not know how, through the Treasury process, nobody really understands it, but we get this budget devoted to healthcare.

That healthcare then covers our population for a vast array of treatments and I will come back to that and how that may be stipulated individually within disease areas when I talk about the guidelines, the NICE guidelines, and give my opinion on how to interpret those, but within that social contract for social insurance, we have a budget limit, and we then have to allocate on the best available information and the best that we can do in terms of trying to meet the needs of -- the population needs, the health needs of the population, and rightly or wrongly one way of prioritising that is to say: let us look at various disease areas, look at those disease areas, and then say currently what is the opportunity cost of treating within those disease areas, and let us say it is £20,000

per QALY, and, therefore, if some new drug comes along then what is the evidence that it is going to displace it.

Now, we are working on averages here, as I said, because we are interested in the average effect for the population at risk within a treatment group and the average cost, because the average cost multiplied by the prevalence of the treatment gives us the budget information. So we are interested in that, and it is the average that we are therefore interested in.

Now, having provided that information, we may say it is well above £20,000 per QALY, and that is where it gets a bit muddied, and that is where other aspects come into play, like is it an innovative new medicine, is it a blockbuster in some sense, is there a special needs group, if you like, an orphan drug which is very expensive, or just now with cystic fibrosis, for example, treatments going through NICE which have been shown to be above the threshold, well above the threshold, but delay the progression of the disease and therefore they have been put into another box which has been mentioned before, the market access box, which says: can we get some negotiated agreement to try this therapy out in the real world, not under the idealised conditions of an RCT, but in a more heterogeneous group

of cystic fibrosis population, to see whether or not there is any inkling that this new therapy will lie somewhere around the £20,000 per QALY.

Now, that is currently going through a patient access scheme just now, run by the Department of Health. These are usually commercially secretive schemes because there is some negotiation over the price and we do not know exactly what the price is going to be, and it will report in 2024.

On top of all of that, if NICE says for all this bundle of reasons we think this should not -- sorry, this should be within the overall social insurance package, individual clinicians can still -- well, there is two things here, actually. Let me go first of all to one other thing.

If you look at the Y axis here, this incremental cost over the comparator, obviously if the comparator has a very high cost, then you could have a very costly drug coming through which is very high priced but still meeting the threshold.

So there was a drug called Sovaldi, I think I pronounced that correctly, which was for hepatitis C, and it is almost 100% effective at washing out the viral load of hepatitis C in an individual patient, very effective, almost 100% effective, but it was £35,000 for

an eleven-week treatment and £70,000-odd for a 24-week treatment, and it was estimated that the budget impact would be somewhere around £1 billion.

So the National Health Service then, England, said to NICE although it is cost effective and under an HTA if it is proven to be cost effective and it meets all the other criteria it is a statutory requirement that the NHS then puts it into its social insurance package.

So the NHS said: well, if we are going to spend a billion on one therapy, we are going to have opportunity costs for a budget elsewhere, and could we delay it, could we delay the access, and in 2014, that is precisely what happened, Sovaldi was delayed in access, and it was delayed so much that combination -- new combination therapies at a lower price were pushed into the NHS social insurance package.

So that is where I say it gets a bit muddied because there is not only parallel tracks in terms of what is going on in regulation of prices, but also the budget impact, and as a result of that there is now a formal requirement that if new therapies come into the NHS, if they cost over £20 million per annum over a three-year period or are projected to cost that much, they have to go into negotiation with NHS England and come to a commercially viable price of the new therapy before it

is uptaken into the social insurance package.

So there is all sorts of muddied negotiations which are run in parallel to these thresholds, but I still come back to the point -- as raised by you -- that I think it is about averages, the best information is on averages. Normally obtained through randomised clinical trials but increasingly through observational studies, what is the average effect of this treatment, what is the average cost, can we work out the budget, but then -- and I will come back to the guidelines, as I say, in a moment, because the guidelines are helping all of us, I think, to define the overall treatment package, and I am still talking about HTAs here.

PROFESSOR WATERSON: Can I just raise another point, because you have talked several times about social insurance and of course there are other aspects of this as well as the NHS, so, you know, people going into care homes either because of their condition or because of their age or whatever. That presumably is not relevant to these studies?

A. Well, it is, because up until -- James would have to correct me on the date, but somewhere around 2014, 2016, it used to be called NICE, it was the National Institute for Clinical Excellence, and it changed its name around about that date to become the National Institute for

Clinical and Social Care Excellence. So it now encompasses social care packages within, because there are, as you are asking, presumably, there is an overlap between the substitution of health and social care treatments, yes.

PROFESSOR WATERSON: Thank you.

THE PRESIDENT: I quite understand why you say statistical evidence matters if one is looking to include in or out certain drugs as a social insurance package, and I am sure we will have debate in closing, not for now, but it is a question of law that we will want to have submissions on, the extent to which when one is answering whether an individual drug is overpriced how it fits into that social insurance package, so I am agreeing probably to 80% as well with what you have just said, but let us reframe the question and suppose the question is simply this: I am looking at the price of an individual product, I am doing so independent of the NHS budget, I am not interested in that, that may be a matter for argument, but let us take that as a given. All I am doing is seeking to work out whether the relationship between price and cost is unfair, and let us take that unfair can mean a variety of things but one of the factors in considering whether the price is an unfair one is the value that it delivers.

In that context, when one is considering the price that is paid for an individual drug, would you accept -- and if you do not, please explain why -- that in computing the value in that case, one ought to be looking to the value to the individual patient given that the drug is not prescribed mindlessly, it is prescribed mindfully by a physician?

A. So if we are outside of the social insurance coverage --

THE PRESIDENT: We are outside it.

A. -- maybe in private care or maybe --

THE PRESIDENT: No, let me be very clear: we are not here to decide how the NHS budget is or is not to be spent. We are here to decide whether a found infringement that a specific set of products have been overpriced is or is not well founded.

So it may be that your social insurance package matters, in which case we will articulate it in the point, but the question that we are here tasked to deal with on this appeal is not that. It is whether a specific price for a specific set of products -- the four phenytoin capsules that we are talking about -- is or is not excessive.

Now, these are very difficult questions, but one of the questions that I think arises -- and that is why I am asking it now -- is whether the gap between cost

and price can be justified by something that we are calling value which is in itself a difficult thing to compute.

Now, you are talking about statistical value, and I understand why, because the budget, if one is talking social insurance, needs to be looking at the aggregate picture, not the specific.

What I am saying is that if the question that we have to deal with is the specific value of a specific product attributed to a specific patient is the game in town, then what is the value of the statistical approach compared to the precise value, because we are presuming that this drug will only be prescribed to someone who actually will benefit from it and, therefore, one needs to ask how much will that particular patient actually benefit.

A. So that is a question, is it not, when do you evaluate the benefit for the patient because very few drugs are complete cures. So if I were a clinician, which I am not, saying to you that you should take this prescription because you have this disease, you would still have an element of expectation around it. It would not be -- it is not a binary this cures you or it does not. It is more what is the effect that it is going to have on you as an individual.

Where would I get that information? Probably from the literature or trial, an observational study, somehow, but it would be based on an average effect. It would not be based on an individual patient response because you would only get that presumably after you paid for the drug.

THE PRESIDENT: Well, Professor, just to understand the level of your knowledge, were you present in court when we heard the evidence from the clinical experts on --

A. No.

THE PRESIDENT: No, you were not. So let me put to you an understanding of how it is that this works.

We have a patient who has been identified as an epileptic sufferer and they have seizures. One has various forms of drug that can assist in alleviating those seizures, and sodium phenytoin is not in the first instance, nor even in the second instance, a drug that is used.

In many cases, the cocktail of line 1 and line 2 drugs will do the job and prevent the seizures. However, there are in some cases -- and it is about 70,000 people -- there are in some cases instances where, in the clinical judgment of the physician, the use of a third-line product -- here sodium phenytoin -- is, in the judgment of the doctors looking at that

individual patient, beneficial in avoiding seizures.

If that is the situation on the ground, of course you are right there is a statistical question, but we are in this case considering a patient who is not responding or not responding satisfactorily to line 1/line 2 products and who is, in the judgment of the doctor, responding to a line 3 product -- here sodium phenytoin -- because you would not keep them on the product if it was not doing the job when previously the cocktail of drugs was resulting in seizures.

My question is simply this: when one is working out the value of sodium phenytoin in that context vis the avoidance of a seizure in a patient who would otherwise have it even with the other drugs, ought one, in assessing value, to be looking at that specific case rather than the overall question of what is statistically beneficial or what is statistically not beneficial?

A. On the basis of being outside the social insurance pocket, I think it is analogous to the patient access schemes that the Department of Health worked, because they are saying we do not have adequate information to pay upfront here, but we may come to a price agreement and follow up with the patient to see whether they are responding to this third-line therapy and, therefore,

try to judge whatever marginal benefit is given to that individual patient against a cost of that benefit, but you will not know the benefit unless -- once you have administered the third-line therapy, unless you follow the patient up, unless you are drawing on information from your clinical experience, in which case I would say again it is an imputed average value and not a specific value to a specific patient, or you are drawing on a wider set of information from the literature or something.

So I think you would have to work out how you are going to prove the benefit for that individual going forward.

THE PRESIDENT: Well, Professor, first of all price and cost and the relationship is the matter we are deciding. So ex ante we cannot make any views about the price and the cost.

What I am putting to you -- and I do not think you are accepting, but I am puzzled as to why -- is that of course we know from 100 years study that sodium phenytoin works, it is a very long-established drug, it is off-patent, it is a generic. We know that.

What we also know, but it is at this point that we move away from the aggregate to the individual, is that certain doctors -- and I am not a doctor; I am just

listening to what the doctors have told us -- they say that in certain instances clinical judgment indicates that patients who are not responding or not fully responding to first and second-line drugs do benefit in the sense that seizures are avoided by the prescription of sodium phenytoin, and that is not done by reference to a statistical sense, except that one knows that sodium phenytoin works in some cases; it is done by reference to the individual patient vis someone who is not responding to line 1/line 2 drugs but may be responding to sodium phenytoin and will only be carried on with sodium phenytoin if it is working vis no seizures.

All I am asking you is, when one is considering the value of the prescription of that capsule to that patient, would you agree that one looks to the value to that patient when determining, in a manner that we will have to decide, the relationship between cost and price and whether it is unfair?

A. I have a proviso to my yes/no answer which is we know phenytoin works and, as I understand the literature, as I have looked at it, there seems to be very big overlapping confidence intervals as to whether phenytoin works with regards to placebo or not. So leave that to one side.

THE PRESIDENT: Yes, I am sorry, but you have strayed well outside your area of expertise on this.

A. All right, leave that to one side.

THE PRESIDENT: So let us go back. We will of course evaluate the medical evidence that we have received, and I am not really very interested in your looking behind that because they are experts in that and you and I are not, so taking that evidence -- and I may have summarised it wrongly, in which case I will be told in closing. There was certainly difference between the two experts that we heard from, but taking my summary is your answer first of all a "yes" or a "no", and then let us have your qualification.

A. Yes. We would have to take account of the value to the individual patient in that particular circumstance as to the benefit that was being attained by the prescription of phenytoin. That is outside of the social insurance bit, because they are not the payer, neither is the clinician the payer. So the payer who is ultimately reimbursing for the phenytoin -- I come back to the fact that we are dealing with a budget-constrained social insurance benefit.

THE PRESIDENT: Entirely fair enough, Professor. What you are doing is you are circling back, and I quite understand why you are doing it and I respect it, you

are circling back to the essential importance of the social insurance element of the NHS provision of drugs because, you are absolutely right, the patient does not pay anything beyond the prescription price. The health service does.

A. Yes.

THE PRESIDENT: Okay, thank you very much.

Sorry, we have gone on rather longer than we should have done. Is there anything more you want to say about this particular slide, Professor, before we break for lunch and resume?

A. Maybe I could just get back to two slides forward. I think we have covered the next slide, if I am correct, really, that is about the opportunity cost, if you go to the next slide {XE7/7/5}. Yes, that is really about the displacement effect of being within a budget and what a QALY does for that budget or how it tries to attain whether or not you are displacing existing treatments with new treatments.

Then the next slide after that {XE7/7/6} I think gets into the definition of the treatment package for the NHS, so if we could go to the next slide --

THE PRESIDENT: That sounds like a good point to break.

A. Exactly. That is what I was going to suggest.

THE PRESIDENT: Excellent. Well, if we are there, because

I am keeping more than half an eye on the shorthand writer, we will rise then, if that is all right. We will start again at 2.10.

Thank you very much.

(1.20 pm)

(The short adjournment)

(2.10 pm)

(Proceedings delayed)

(2.14 pm)

THE PRESIDENT: Professor, before you resume, we have been discussing the point I was putting to you just before the short adjournment and I would like to put it to you with one variant to see if it makes a difference to your answers, and it is this: I was putting to you that the individual patient was the person that one would look at in order to compute value as a justification for the gap in our particular enquiry between cost and price.

Now, of course, we are not really talking about a single patient, but what we are talking about is a cohort of patients which will have certain common characteristics of the single patient that I was putting to you. In other words, we have X thousand epileptic sufferers who, by reason of clinical judgment, are on a third-line drug which happens to be sodium phenytoin because, in the clinical judgment of the doctors

prescribing it, it is good for them to avoid seizures, and when I was speaking about the individual patient, I was really and inaccurately talking about the cohort, and my point is, though, does that make a difference to the answers you gave me in the sense that the cohort that we are talking about has not been randomly selected, they have been quite consciously and in a good way biasedly selected by the clinical judgment of the physicians who have chosen to prescribe to them sodium phenytoin capsules?

A. So again, we are talking about being outside of the social insurance fund.

THE PRESIDENT: Yes, I have your point about the social insurance fund. We are outside that, though I strongly suspect we are going to be coming back to that in closing, so we are just talking about the question of price, cost and how we attribute value to the thing that is being prescribed.

A. No, it does not change my position, except for the fact that with a cohort there would be a distribution of health benefits rather than a single health benefit.

THE PRESIDENT: Indeed, I quite take that point, but it would be a distribution across a group of people that would have similar characteristics.

Now, I am not going to enumerate them because

neither you nor I are expert enough to do that, but there would be certain characteristics that would cause the doctor to say: I advise you, patient in the cohort, to have this form of drug in addition to the others that you are taking?

A. Yes, so there would be a distribution, and just to be absolutely clear, my response is that value would be elicited by that distribution of patient cohort, and at this point nobody is paying for it.

THE PRESIDENT: That is going back to social insurance, of course.

A. Or generally nobody is paying for it. The clinician is not paying for it, the patient is not paying for it, we have not got price in there, it is just value.

THE PRESIDENT: Professor, we are moving well beyond, I think, your expertise, certainly well beyond the questions that I am asking you. I take your point --

A. In terms of what expertise do you mean? The effectiveness, or --

THE PRESIDENT: Professor, we will draw stumps there, I am not asking you that question. If someone else wants to, they can.

A. All right.

THE PRESIDENT: Do proceed.

A. So just to recap, then, I was only talking about the HTA

assessments that NICE make. They make it on the basis of some kind of opportunity cost of a unit of health benefit being provided by the NHS.

Within that cost effectiveness threshold plays some role in making a decision amongst a set of criteria to say whether or not a new therapy, a new patented therapy would come into play in the NHS, and as part of the treatment cost in that assessment, the price of the new therapy has already been determined through the list price but feeds into the calculation.

Now, if we move to the -- and if we are fine with all of that, that is the HTA process. The second process is the next slide, which is the guidance process {XE7/7/6}.

Essentially I think of this as the NHS being a social insurer and the guidelines process being concerned with trying to look at the treatment benefits and trying to define those on a disease area by disease area, and there cost effectiveness may or may not be part of the guidance, there may not be enough evidence or enough data to allow the guidelines committee in the disease area to come up with cost effectiveness evidence, but certainly if cost effectiveness is used, it would only be part of the much wider set of criteria that goes into the guidelines which are really, in my

experience, which is quite narrow in type 2 diabetes and twice being on these committees, is quite heavily dominated by the clinical discussion, but cost effectiveness will come into it and again, it will be related to the opportunity cost, but, as James said, James Hawkins said, it would also include patient preferences, for example, coming into play.

However, the guidelines do not really consider price at all. Generics and branded drugs might form part of the package in the disease area and will be discussed, but the price will come from the list price of the branded drugs and for generics it is usually that the generics are on the market in any case and, therefore, the price will have been set by the drug tariff.

Just as an aside, to talk about the particular example that Dr Skedgel gave of levetiracetam, I think it was called, which is one of the drugs in the epilepsy package, he said that they said it would not be cost effective at the current price in 2011, feeding into the 2012 guidelines for epilepsy, but if it dropped by 50%, it would be considered cost effective.

Now, that, to my mind, was not giving a steer on pricing at all, it was reflecting the fact that levetiracetam was coming off-patent in 2011 and, therefore, the guidelines committee, the clinicians are

very aware of these movements, was thinking: well, actually, we will see a drop in the price of this particular treatment which would probably make it cost effective, and indeed that happened. If you take the 250mg capsule for levetiracetam it dropped from £28 to £1.28 over a two-year period, so it was a much greater than 50% drop because of the movement from a patent into a generic compound.

THE PRESIDENT: Yes. You said a moment ago the guidelines do not really consider price at all. I think what you meant was that the guidelines take price as an input --

A. Yes.

THE PRESIDENT: -- and do not vary it or say what is the right price or what is the wrong price, they simply take it as an input into their calculations of cost benefit?

A. Absolutely, but they do want to future-proof the guidelines and, therefore, they recognise that that price would have changed and we know from various studies and reports that, as generics come on to the market, generally we see a drop in price. There is an Oxera report commissioned by the generic manufacturers in the UK for across 280-odd --

PROFESSOR WATERSON: We have it.

A. Do you? That says essentially 70% drop in price after you move from a patent to a generic which drifts back up

to 20% price drop after a while.

We know in other areas like in statins around about 2012, atorvastatin came off-patent, and that made the budget in the cardiovascular disease area went down, down, the whole budget went down by about 50% as statins came off-patent. Atorvastatin itself had a £330 million budget associated with it, and it dropped to about £3.3 million after it was associated with this drop in generic price.

THE PRESIDENT: Would you say, Professor, that given that NICE takes the prices as inputs and does not seek to vary them that it is an implied assumption of the NICE system that the input prices are market prices and to be relied upon as fair outcomes of the market, or would you say that that was stretching matters?

A. So if we are talking about the non-branded generics --

THE PRESIDENT: Well, I am talking about any product that is evaluated by NICE and, if you want to draw distinctions between different sorts, by all means do.

A. For branded products it would take the list price and the list price will have been negotiated somehow. In fact, if you go to the next slide {XE7/7/7}, it may be quite helpful.

If you take the two processes, HTA and the guidelines, the HTA process, as I have said, is really

concerned with assessing branded products, patented products in particular.

When these list prices will be fed in as an input to the NICE evaluation to look at the opportunity cost of this new technology coming into play through a new treatment, it may be that there have been some price discounts already negotiated from the manufacturer and the Department of Health with regards to the list price, and that is quite important because, as I said, list prices are used as benchmarks elsewhere in the globe, so they want a list price set, but then they might negotiate down, so that is not really a market impact there, it is a negotiation between manufacturer and the Department of Health.

Then it will feed into the NICE HTA process where they will use a bunch of criteria, a set of criteria for the decision-making, including the threshold and the threshold is quite important, obviously, and if the new therapy meets all their criteria, then there is a statutory duty for the NHS to pick up this new therapy although the proviso is, as I said, with Sovaldi, the drug for hepatitis C that led to another formal engagement over the budget impact that any particular treatment was going to have, and if it is over £20 million over a three-year period -- per annum over

a three-year period there is another negotiated down price, and then ultimately the people who pay, the purchasers in the NHS, are the clinical care groups or the integrated care bodies as they are now called, and they are essentially groupings of GPs who have a budget given to them, disbursed on a formulaic basis by the Department of Health, and even at that stage the CCGs may then again negotiate further down in price to allow their budgets not to be overwhelmed by any particular new treatment.

THE PRESIDENT: I see. That, I think, is something which is new. My understanding was that CCGs, as they then were, were price takers and were not price makers.

A. So that is the HTA process for new drugs, and as I say, that process has never evaluated or assessed generics to my mind --

THE PRESIDENT: No, I am looking at the two boxes on your slide. So you have branded drugs?

A. Yes, so that is the top line, the top row.

THE PRESIDENT: Okay, so we ought to correct your last box to say NHS or, as they then were, CCGs, so it is not just the Department of Health, it is DoH plus CCG that might negotiate the reimbursement price?

A. No, you are looking at the bottom row, I think. The top row does say:

"The NHS may negotiate the reimbursement price it actually pays ..."

THE PRESIDENT: Yes, that is the row I am looking at. Sorry.

PROFESSOR WATERSON: You are saying NHS as --

A. CCGs.

PROFESSOR WATERSON: Yes.

THE PRESIDENT: Right, okay.

A. Sorry, so replace -- CCGs may --

THE PRESIDENT: So NHS replace the CCG?

A. You could call them NHS CCGs may negotiate the reimbursement price.

THE PRESIDENT: Yes, of course, Professor, I understand that NHS is broader descriptor of items that are in there, but what you are doing is I think you are saying that if I want a more granular understanding of what NHS is, I should be inserting CCG, not Department of Health?

A. Fine, yes.

THE PRESIDENT: Okay. So it is your evidence, then, that the reimbursement price, which I understand is based on the drug tariff -- have I got that right?

A. No, no, hang on then.

THE PRESIDENT: Right.

A. So that is the HTA process, that is based on list prices. When we go to generics, that is the row below.

THE PRESIDENT: Okay, so the reimbursement price is nothing to do with the drug tariff at all?

A. Not for new therapies which are assessed through the HTA, the top line here.

THE PRESIDENT: Okay, so do we need to draw a distinction between HTA and branded drugs?

A. HTAs assessed branded drugs.

THE PRESIDENT: Right, so there is a complete coincidence between HTAs and branded drugs?

A. Not coincidence, I would say. The HTA processes is there to assess branded drugs.

THE PRESIDENT: Branded drugs?

A. Yes.

THE PRESIDENT: Okay. Branded drugs do not appear as lists on the drug tariff?

A. No.

THE PRESIDENT: They are not listed there?

A. No.

THE PRESIDENT: Okay.

A. And the drug tariff is an additional --

THE PRESIDENT: So the drug tariff --

A. -- regulation or negotiation, if you like, between the Department of Health and the manufacturers, but it is confined to generic products.

THE PRESIDENT: Right, so it is your bottom line?

A. Yes.

THE PRESIDENT: Okay.

A. Does that make sense to you?

THE PRESIDENT: No, it makes perfect sense. I am not sure that it will reach uniform agreement in the court, but it is very helpful to have it out there because we are obviously tasked with understanding how all this works, and you have very helpfully corrected what is my present understanding of how this works. So it is on the record. I hope that someone will expose the correctness or otherwise of that because it does seem to me that it matters, and what you have done is you have very helpfully confined the role of the drug tariff to your bottom set of boxes.

A. The drug tariff would be negotiated between the Department of Health and the generic manufacturers and by the time it gets down to the CCG level as the last box in the bottom line says, the GPs are then price takers, they have to take the drug tariff as a given price and they cannot negotiate further.

THE PRESIDENT: Thank you.

A. That said, just to be absolutely clear, for the HTAs, the drug price is an input into the cost effectiveness and within the guidelines if a cost effectiveness were undertaken, it is not necessary, it may not be, if it

were, the drug tariff price would be an input into that cost effectiveness analysis as well.

THE PRESIDENT: Well, thank you very much.

I do not know who is cross-examining the Professor. Is that you, Mr O'Donoghue?

MR O'DONOGHUE: Yes.

THE PRESIDENT: We have, as you will all know, previously written to the parties saying that an understanding of the drug tariff and the various schemes that exist under it, PPRS, the other schemes, is something that we would like to have. It sounds as if you have the source in the witness box for that. It would, I think, be helpful if you could ensure that we have on the record exactly how this works so that we can understand it in the future.

MR O'DONOGHUE: Sir, it is topical. The note the Tribunal requested I think is being finalised today and hopefully will find its way to the Tribunal.

THE PRESIDENT: That is very helpful. If that note happens to be ad idem with what we have just heard from the Professor, then that is great; if it is not, then I think we do need to stress test the note and the evidence that we have just heard.

MR O'DONOGHUE: Sir, we will do that.

THE PRESIDENT: I am grateful.

PROFESSOR WATERSON: Can I just check, just so that we are clear, when you talk about branded drugs and the HTA process, there is also this other category which is relevant to phenytoin where the drug is branded but a generic, or it has a label but is a generic.

Is your understanding that that would come under the lower set of criteria?

A. That is my understanding because I cannot think of any example of a branded generic which has been through an HTA process.

PROFESSOR WATERSON: Thank you.

A. Anything else on that slide? If not, then we can progress to the next one {XE7/7/8}.

In this one, I am just really setting out a couple of things. One is that the NICE guidelines are therefore non-statutory recommendations which are given to the NHS on the treatment package within a disease area which is defined by these guidelines which are recommended to clinicians and saying essentially: this is the guidance that we are giving to you in terms of your clinical practice.

Now, they are only recommendations. The clinicians may or may not hold to these recommendations, but at least it gives them a set of evidence-based policies on their clinical practice to which they may refer.

That means that, for example, the generic prices and generics themselves are generally on the market when they are considered across these guidance disease areas, and it is also the case that there would be no point in a generic drug pricing to a threshold, the threshold of £20,000, which is the common threshold the guidelines take, they do not take anything above £20,000, that tends to be part of the HTA process, but there would be no point in generic pricing to a threshold because first of all, they are already on the market and it has taken that competitive pressures are pushing these prices down.

I did just an intellectual exercise for, partly my benefit, hopefully for the court's benefit, the Tribunal's benefit. If I took one particular generic, metformin, it is used in type 2 diabetics, it is an extremely common first-line procedure and based on the NICE guidelines I looked at the combination therapy of metformin used as a monotherapy in first line and then with sulphonylurea as second-line and then insulin as third, currently metformin is priced at £22 per annum, it is about 6p a day, and it is associated with a comparator of do nothing. If you did not do metformin as continued therapy over an 18-year period but then a second therapy of sulfonylurea and then insulin as

third therapy, it is associated with a cost per QALY of about £2,000.

If you wanted to get that metformin price up to a price that was consistent with the threshold of £20,000, you could raise metformin up to £11,000 from -- as a price per annum from £22. You could raise it to £11,000.

That would break the bank essentially, because there are 8,500 individuals on metformin in the UK, 8,500 multiplied by the 11,000 which would be the threshold consistent price would then give you 9 billion being spent on metformin on a single therapy, and the NHS only has 18 billion.

So it is a kind of nonsensical example to show that generally speaking, even if you accept that generics could price to the threshold, it would not really wear any -- it would be nonsensical to do so, and I am raising it partly because, as you have seen in Dr Skedgel's submission, his price comes out at about £20,000 per QALY for phenytoin. Of course not to compared to do nothing but compared to another drug.

That said, I do not think guidelines play any role whatsoever in determining product or reimbursement prices. They are there to really determine the treatment package which is consistent with the delivery

of the social insured NHS. So it is a recommendation but these unbranded generics have never been part of the HTA process as far as I know, and within the guidelines process they are only one small part of the overall consideration.

Next slide, please {XE7/7/9}.

Now, in terms of whether QALY analysis relates to economic value, I think it tells you very little in terms of the generics because, as I have said, generics are priced through competitive pressures and they feed into the guidelines.

For new therapies, there may be a tendency, and increasingly there will be because the new VPAS listed price regulations are consistent with -- are trying to be consistent with drugs pricing to within the 20,000 or to 30,000 per QALY threshold, so the Department of Health, NHS and NICE are trying to get some consistency between these thresholds and the VPAS regulations, the voluntary scheme through which the listed prices for branded therapies are currently defined, but it has to be said that in pricing to any threshold this is dealing with a situation where you have already got a budget, the NHS has already got its overall budget, and the budget is attempting to maximise the overall health of the population that it is covering.

Next slide, please {XE7/7/10}. And the HTA process is only dealing with patented drugs, it is really only dealing with branded, patented drugs. So of course you have got a monopoly situation because you have got a patent, so, in trying to think about how the threshold comes into play and whether manufacturers price to that threshold, then what you are trying to -- I think what NICE is trying to do is trying to get the new drug prices consistent with -- and these are patented drugs which have monopoly power obviously -- new drug prices consistent with the overall NHS budget as based on a threshold which gives manufacturers information about the opportunity cost of existing therapies within the NHS which they currently fund.

So if anything, it is telling you about the willingness to pay in some broad way about the purchaser's willingness to pay, the NHS willingness to pay, as based on the opportunity cost threshold value of £20,000 to £30,000 per QALY within the HTA process for branded drugs, for monopoly drugs, and of course, if the manufacturer does price to that threshold, then they are getting all of the producer surplus associated with that purchase price from the NHS. So they could, for new branded drugs, you could say -- and I think we will given this alignment of VPAS and NICE thresholds which

NICE, NHS England and the Department of Health are now pushing, we will see prices of new therapies being pushed to that £20,000, £30,000 per QALY threshold, but that will mean that the manufacturer will get all of the producer surplus there.

They may not -- sorry, go on.

THE PRESIDENT: You said a couple of minutes ago, you used the phrase "manufacturers price to that threshold", referring to the £20,000 threshold. Now, that is actually quite a complex process, is it not, because what they need to do is they need to know what they are charging for their treatment and what QALYs that treatment is going to deliver, all of that compared to the substitute, the old regime and what price that has and what QALYs that delivers.

So you have a complex range of inputs, the two simultaneous equations, as it were, the new and the old, and you have, in relation to each, cost and QALYs delivered through that cost.

Now, how much of those parameters will be known to the manufacturer of the new product so that they can, in fact, price to the threshold or how much of it will be no doubt highly informed guesswork?

A. So they will definitely know about their own product and they will have clinical trial evidence and they will

have gone through the modelling for all that and been able to price to the £20,000 per QALY threshold if they make assumptions, informed guesses in your phrase, assumptions about what is happening with the comparator.

THE PRESIDENT: Okay, pausing there, obviously they will know the price they intended to charge, that is self-evident because they will be setting it.

A. Well, that will fall out of the calculation, right.

THE PRESIDENT: If, of course, you are right and they are pricing to the threshold, then absolutely, I take that.

A. Yes.

THE PRESIDENT: So it will be an output rather than input, but that is something they completely control.

A. Yes.

THE PRESIDENT: So the question of knowledge does not arise.

A. Yes.

THE PRESIDENT: Turning to the QALYs that the new product under trial delivers, is that something that is a matter of discussion between the pharmaceutical company and NICE, or will the pharmaceutical company have to try and second-guess the number of QALYs that NICE will evaluate the treatment progresses, or is the system so transparent and so predictable that I can say as a pharmaceutical manufacturer: this product is going to deliver that number of QALYs?

A. It is something that the manufacturer will have to persuade on the body of evidence, data, NICE about. So they will have designed their trials in that way, they will have to use the specific or may use the specific instrument, the NICE supports for estimating quality of life adjustment weights, to survival probabilities, and they would have to be transparent in all of their assumptions to do that.

Then on top of that, they would have to undertake this uncertainty analysis based on probability, sensitivity analysis, simulations of the parameter values around the health benefits that may be gained from their new technology, and then they might also have to produce evidence on, well, if we change structural assumptions in our model, this would give us another range of values.

THE PRESIDENT: I appreciate it is a very complex process, but I got from that answer -- one of the things I got from that answer was that there is a dialogue between NICE and the pharmaceutical companies such that they are working collaboratively, one might say, in terms of establishing what the QALY output of this particular treatment will be.

A. Now, we are only talking about the branded monopoly --

THE PRESIDENT: I appreciate -- we can go back to your top

row, I am only talking about the top row.

A. No, no, I wrote -- in the HTA process, and to help the manufacturer there are very publicly available methodological statements about how all this evidence should be put together, and NICE also allows manufacturers to talk to them prior to the submission but not all manufacturers take up that offer.

THE PRESIDENT: I understand, but if I am a manufacturer that is seeking to price to the threshold, then there is a means for me to ascertain with a reasonably high degree of confidence what QALYs NICE will put into the equation when they are doing the assessment themselves.

A. So if the standard therapy which would be the reference case --

THE PRESIDENT: Well, let us come to the reference case in a moment. We have four parameters, Professor.

A. All right.

THE PRESIDENT: We have the new treatment which is under assessment, we have the price of that, and we have the QALYs that it delivers. Then we have the old benchmark therapy which may be no therapy at all but is the benchmark which itself has a QALY number and a cost.

So let us leave that second one alone for the moment, we will come to it. Let us stick with the data that one has for the new product, because what I am

trying to work out is how easy it is for a pharmaceutical company to price to the threshold, to take your phrase.

So we are agreed, I think, that the price will be the output of this process. What we are trying to work out is the workability of it.

So the next parameter on the new thing is QALYs that it delivers and I think what you are saying is that if you are a pharmaceutical company that wants to work out what QALY value NICE will attribute to the product, then you can, to a fairly high order of predictability, work that out?

A. Yes.

THE PRESIDENT: Thank you.

Now, staying in the shoes of the pharmaceutical company that is trying to persuade and trying to price to the threshold, what will the pharmaceutical company know about the benchmark, the old form of treatment? Will they know what cost and what QALYs NICE will attribute to that? In other words, will they know the parameters of the benchmark?

A. So there may be a standard therapy, there may be a range of standard therapies, and for some particularly complex disease areas like oncology, there may be a range of standard therapies which will affect the population that

the manufacturer has targeted.

So they may not know precisely what the reference benchmark case is going to be, but they will have to make a guess, and they can open a dialogue with NICE about that, and then in terms of the QALYs that the benchmark has ascertained, they may or may not know, and they will have to make some modelling assumptions or they will have to take previous HTA submissions to try to find that out. So it is an educated guess at that level.

THE PRESIDENT: That is very helpful. Educated guess, and that is because if the pharmaceutical company were to ask NICE what are the parameters of your benchmark, NICE would entirely understandably say: well, that is information we will keep to ourselves because otherwise you will be able to price to the threshold automatically in every case?

A. Yes, I think that is true to say that. They may nevertheless in some instances have very good educated guesses. They may not price to the threshold in any case because of the other aspects I have put in the slide. There might be a budgetary impact, so they might fall foul of this 20 million per annum over the next three years, or there might be close substitutes to the therapy which are about to come online.

THE PRESIDENT: I quite understand we are not talking about the whole system here, but if I can just reframe what I have got from your phrase "pricing to that threshold", what I think you are telling me -- and do correct me if I am wrong -- is this: that if I am a manufacturer who is minded to generate a price that is likely to pass the NICE threshold, although it is not an exercise in certainty, and although there will be some information that I will have to estimate rather than know, it is something which I can, to a reasonably high order of certainty, establish if I am minded to do so?

A. In most instances, yes.

THE PRESIDENT: I am very grateful.

A. And that is for branded products which have a patent monopoly.

THE PRESIDENT: No, indeed.

A. Correct.

THE PRESIDENT: Thank you very much.

A. But as I say, there might be other reasons and considerations which --

THE PRESIDENT: I quite take that point.

A. Right, but of course that does not mean, going back to the point that I was making at the beginning about does this tell you anything about competitive producer surplus, it does not really because we are dealing with

a monopoly situation here, and therefore the HTA QALY considerations under the HTA process, even if they are pricing to a threshold, does not mean that these prices are going to be anywhere near competitive prices.

Next slide, please {XE7/7/11}.

Indeed, if you then thought about the generics and guidelines, generics of course are already on the market and meant to be being open to competitive pressure in any case.

This slide is the only slide I am going to talk about Dr Skedgel's specific work. I think that has been brought out by his own presentation and James Hawkins' in very great detail. The only thing I would say is that I am not criticising the intrinsic quality of the work. I think the work was put together under data and time constraints, so I am not going to criticise the intrinsic quality, but does it meet the NICE HTA standards? I do not think it does, and I do not think it does for various reasons. The first thing, of course, is that as a generic it would not be part of the HTA process, it would be considered under guidelines where maybe the assumptions that are brought to bear in a cost effectiveness model are slightly lower, but in any case, cost per QALY assessment within the guidelines is nothing to do with setting the price, the price

already is an input here.

Then, even if you accept the use of a cost per QALY model to tell you something about generic prices, which I do not, his own calculation shows basically a 50/50 chance of it being cost effective at £20,000 per QALY, which is the guidelines threshold, and so I think there is a large degree of uncertainty. We are probably in discussion at the guidelines committee, the clinicians would take over, and that certainly seems to be what happened when we look at the NICE documentation of the guidelines for drugs in this area, and also there is some fundamental structural assumptions which I disagree with on top of the sensitivity analysis, but that is all documented in my written statements.

That is the end of the slide deck.

THE PRESIDENT: Professor, thank you very much. We look forward to seeing you again when you are cross-examined, but that is it for now. Thank you very much.

THE WITNESS: Thank you.

MS MORRISON: I think it falls to me to call Mr Hawkins back for his cross-examination.

MR JAMES HAWKINS (recalled)

THE PRESIDENT: Mr Hawkins, do sit down. Welcome back. You are going to be led straight into cross-examination because your reports have already been put into

evidence, and you will be tendered therefore straightaway for cross-examination by Mr O'Donoghue.

You are not going to be re-sworn because you are already under oath, so I will leave you to Mr O'Donoghue.

A. Thank you.

Cross-examination by MR O'DONOGHUE

MR O'DONOGHUE: Mr Hawkins, I am conscious there is a cast of dozens. No one has been shot yet. Just for your benefit, Mr Hawkins, I am counsel to Pfizer who is one of the two appellants in this case, just so you understand where I am coming from. I will not be underarm bowling if that is of any assistance to you.

Now, just to put my cards on the table as to the confines of your evidence, can we go back to this morning's transcript at page [46], please. It is at the bottom of the page, {Day14LH1/45/22}.

The President says:

"... a great deal in his evidence and ... teach-in that you will be wanting to put ... I do not know how quickly, but he may come to the limits of his factual understanding, the extent to which he can do no more than say this is what NICE has done, and I can assist no further."

Do you see that?

A. Yes, I can see that.
Q. So Mr Hawkins, you are here as a factual witness, and can we just go to your first statement. It is {XC1/6} and we start at page {XC1/6/3}, please. Do you see at the top, 9:

"I make this witness statement to address factual points ..."

Do you see that? Then at the end at page {XC1/6/14}, you see the declaration you signed, and you see:

"I understand that the purpose of this witness statement is to set out matters of fact of which I have personal knowledge."

Do you remember signing that?
A. Yes.
Q. So what I want to focus on with you is matters of fact to which you have personal knowledge; is that clear?
A. That is clear, yes.
Q. Now, just to unpack that a little, you have only worked at NICE for, I think, about 18 months; is that correct?
A. I have worked at NICE for, yes, 18 months, about 18 months.
Q. At least for present purposes, the primary piece of work you have assisted with is the 2022 guidelines?
A. Yes, that is correct.

Q. Now, you are obviously aware that there were guidelines from NICE in 2012 and again in 2004. Now, beyond reading what those guidelines and associated documents say, which any of us can do, you are not in a position, based on your personal knowledge at NICE, to assist the Tribunal in relation to those two sets of guidelines?
A. I did not work on either of those guidelines.
Q. Therefore you have no personal knowledge of what NICE did or did not do beyond reading the relevant documents?
A. That is correct.
Q. Now the final point before we get into some more detailed matters: are you aware that in this case the infringement period covers 2012 to 2016?
A. I was not aware of that. I may have read it at some point, but I had forgotten it.
Q. You will understand the reason I am putting this to you, because obviously in 2012, neither Pfizer nor Flynn could have had the clairvoyance to understand what NICE might or might not say in 2022. You understand that?
A. I understand that.
Q. Now, if we go back to your decision or your evidential hierarchy pyramid in the teach-in, I just want to clear some of the ground in terms of the evidential building blocks. You are aware that phenytoin has been prescribed consistently for almost a century?

A. I am aware of that, yes.
Q. At the time of the infringement, there were around 57,000 patients taking phenytoin in the UK every day, phenytoin capsules every day.
A. I was not aware of that, but it seems believable.
Q. To the capsule number we need to add the tablets which is about a quarter, so roughly 70,000 patients at the relevant time?
A. I was not aware of that, but that seems believable.
Q. Of the patient population, at least then, about one in ten patients were on phenytoin sodium capsules or tablets.
A. I do not know, I would not have that knowledge.
Q. Fair enough. Now, something you will know, I would suggest, based on the clinical discussions in 2022, is that there is a clinical consensus that phenytoin sodium is an effective AED treatment.
A. I believe that is reasonable.
THE PRESIDENT: Mr Hawkins, as counsel has made clear, you are a witness of fact and not an expert, so "I do not know" is a perfectly acceptable response and if you want to say that, then that is absolutely fine. So do not try to evaluate the believability or otherwise of the points that Mr O'Donoghue is putting to you, that is a matter for me. We are really interested in your

evidence, but only the evidence that you can give.

So if you do not know the answer, then the most helpful answer you can give is: it is outside my knowledge.

I hope that --

A. I was not aware of those figures, I did not have them in my mind.

THE PRESIDENT: That is absolutely fine, and to be clear, if you cannot remember, this is not a memory test, we can certainly enable you to access documents provided you are refreshing your actual recollection, then if you need to see certain documents of course we will try and get them up there, but at the end of the day what we are interested in is your knowledge, not what is said in documents which we can all read for ourselves.

I hope that helps. I do not want you to be uncomfortable about being asked about things that you feel you cannot contribute towards. So that is all I am saying.

A. Thank you. I will bear that in mind.

THE PRESIDENT: I am grateful.

MR O'DONOGHUE: Now, again, you must know -- because you were involved in the 2022 guidelines where clinical issues were part of the evidential hierarchy that ultimately led to phenytoin sodium being recommended, so

you will recall from those discussions of which you were part or at least made aware that clinical effectiveness was part of the evidential hierarchy leading to the recommendation of phenytoin.

A. Sorry, I do not understand the question.

Q. Well, if we go back to your teach-in slides, your pyramid {XC3/1/37}, you list various pieces of evidence, and one of the pieces of evidence in red at the bottom is "expert opinion", and you also talk about "individual case reports" and "non-randomised controlled trials". So here we have pieces of either clinical evidence or clinical input which formed part of the evidential hierarchy, and the point I am putting to you is that in 2022 at least some of this evidence fed into the decision to recommend phenytoin sodium.

A. In our evidence review, we only looked for randomised control trials, which the only evidence we found for that was Cramer for the greater than 50% deduction in seizure frequency and for withdrawal due to adverse events. We did not consider any other evidence in making those recommendations.

Q. We will come to Cramer.

Now, you are aware that phenytoin was recommended by NICE in 2004, 2012 and of course in 2022.

A. Yes, I am aware of that.

Q. I want to start by focusing on how NICE considers value for money. If we can start with the legal basis for this, the Health and Social Care Act. It is at {XN8/8/266}. It is section 233. So (a), NICE must consider:

"The broad balance between the benefits and costs ..."

(b):

"The degree of need ..."

Then (c):

"... promoting innovation ..."

So that is the starting point.

A. I am not an expert in law, but NICE does take all those points into consideration.

Q. Thank you. Now, in very simple and general terms, the overall objective from NICE's perspective is to consider whether a treatment constitutes an efficient use of NHS resources.

A. Broadly, yes.

Q. Now, can we look at the language NICE itself uses, if we can go to {XF3/8/94}, please, you see at 4.7.22 we see the phrase:

"... a good use of NHS resources for a given threshold (for example, £20,000 and £30,000 per QALY gained) ..."

So in NICE's language it is testing whether the product or technology or treatment cycle is a good use of NHS resources.

A. So this is from the technology appraisals manual.

Q. Yes. It is a NICE document.

A. Yes.

Q. Now, you say in paragraph 20 of your first statement, Hawkins 1, the typical method by which NICE carries out that assessment is the QALY and ICER metrics. Let us have a look at that in fairness to you. It is at {XC1/6/5}.

You see in 20 the reference to "QALY". At the bottom of the page you say:

"All relevant costs to the NHS and personal social services directly related to the intervention ... are calculated."

That is a point you picked up on in your teach-in.

Now, can we look at what Dr Skedgel says about this. It is in his position paper. It is at {XE6/1/3}.

You will see there in paragraph 10, if I could ask you to read, that Mr Hawkins.

A. Sorry, did you say paragraph 10?

Q. Yes. And the two sub-paragraphs.

A. Yes, sure. Read out loud?

THE PRESIDENT: No, no, just read it to yourself,

Mr Hawkins.

A. Oh, okay. (Pause)

I have read it.

MR O'DONOGHUE: Now, I understood from your teach-in, but tell me if I am wrong, that you essentially agree with this?

A. Other than the bit about residential care home costs, professional care workers and social care workers costs being missed, they are always in my analyses, I do largely agree with this, yes.

Q. So you would include those?

A. I would include those costs, yes.

Q. So it includes costs and cost savings and therefore the costs avoided by the NHS by adopting one particular treatment path versus another; correct?

A. Yes, that is correct.

Q. Now, we have seen multiple references to the £20,000 QALY threshold, and, as a rule of thumb, where the ICER is below 20,000, that is considered to be cost effective; correct?

A. Very broadly, yes.

Q. Now the threshold comes from NICE itself, there is some debate as to its genesis, but we can say on the basis it has been consistently applied for 24 years that it represents the threshold at which the Department of

Health has decided that the benefit derived from a drug for the patient represents a good use of NHS resources?

A. Yes, I would agree with that.

Q. To put it another way, at that level of ICER, there is sufficient benefit to justify the expense?

A. If you are certain of that estimate, yes.

Q. Now, if we go back to your statement at {XC1/6/6}, Mr Hawkins, it is paragraph 22, you make the point there that if you are above 20,000 at the ICER, then the other factors you list come into play, and depending on the assessment of those factors, there may still be a positive recommendation. In other words, judgment is needed according to these criteria above a £20,000 ICER?

A. That is correct, yes.

Q. Now, the first factor you mention is uncertainty, and do I take from what you say that the presence of some uncertainty would not necessarily be defeating and that NICE would, as best it could, try and form a judgment about the degree of uncertainty in terms of its decision-making?

A. Yes, you are never going to be 100% certain, there has never been a technology appraisal or guideline or economic model where there has been 100% certainly. There is always a degree of uncertainty.

Q. I think you said yesterday in the teach-in, I quote "we

often have less than perfect information". That is the reality, is it not?

A. That is the reality, yes.

Q. I now want to move on to NICE and drug pricing, which is a point that both you and Professor McGuire focus on quite a bit.

Can I start with a few basic points. NICE was established 24 years ago as an executive non-departmental public body?

A. That is correct, yes.

Q. And NICE is an international leader in this area: the QALY metrics and similar metrics are now routinely adopted by many other western countries to make decisions on health economics?

A. That is correct, yes.

Q. Now, as you said in your teach-in, one of NICE's roles is to promulgate guidelines and to conduct technology appraisals designed to assess whether drugs or treatments offer good value for money to the NHS as the ultimate purchaser of such products, and for these purposes, NICE's role is to provide an evidence-based independent source of advice to the NHS on which drugs or treatments are worth paying for?

A. That is correct, yes.

Q. I think you said yesterday in the teach-in that NICE,

and I quote "has the largest publicly owned library of guidance in the world"?

A. That is correct, I did say that.

Q. Now, in simple terms, as I think we have established, NICE seeks to measure value for money for the NHS, does it not?

A. I think that would be fair to say, yes.

Q. Now, can we look at one of NICE's reports on this. It is {XD1/6/605}, and it is at the top of the page.

Now, Mr Hawkins, the documents in this case are electronic only. It will be a bit of a blizzard. In fairness to you, if you want to see something earlier in the document or later, just tell me. I do not want to sort of hem you in in that way, so if you want to see the context, let me know. I want to be perfectly fair to you.

If you see at the top, this is the 2012 AED guidance and it says at the top:

"It is important to investigate whether health services are cost-effective (that is, value for money)."

Then they go on to explain, to unpack that a little bit, and then further down the page you will see:

"The intervention costs less than 20,000 per... (QALY) gained compared to the next best strategy."

So we see in particular under (b) there is an

explicit reference to the £20,000 threshold. It is in this context a measure of value for money.

It is the point at which NICE is saying that the value for money provided by the drug is good value for money or a good use of NHS resources.

A. Sorry, I am just reading the whole paragraph.

Q. Please do. (Pause)

A. So, yes, that is making reference to the £20,000 threshold, inverted commas, for (inaudible) deciding value for money.

Q. Excuse me. It is NICE's economic measure of value for money?

A. Yes.

Q. Now, something which I think is uncontroversial, if a drug passes a NICE technology appraisal assessment, the NHS is legally obliged to then fund the drug at that price, is it not?

A. That is my understanding of the law.

Q. Now, can we look at how this works in practice. Go to {XF3/49}, please.

So this is a commentary on, as you will see, value-based pricing for medicines. It is an international study of the UK and other countries.

Now, Mr Hawkins, if we start on page 1 under the introduction on the right-hand side, do you have that?

A. Yes, I have that.

Q. It says:

"Value-based pricing ... is a well-established pricing method for goods and services. VBP dictates that the price of the commodity should reflect the value to the buyer rather than the actual costs of production augmented by the profit margin. In principle, [value-based pricing] for drugs means that prices charged to third payers are mainly linked to the drug's value and that impact on budget is a second-order driver of price regulation."

Then further down:

"However ... [value-based pricing] for pharmaceuticals has been for years considered superior compared with cost-plus methods of price determination ..."

They go on to make points about heterogeneity.

Now, if we then go forward, Mr Hawkins, to page {XF3/49/4}, you see on the bottom left:

"VBP where cost-effectiveness is the driver."

Do you see "the United Kingdom", do you see that?

A. Yes, I can see that.

Q. "In the [UK], NICE explicitly bases the definition of value on cost-effectiveness and defines explicit [willingness to pay] thresholds ... an additional QALY

gained through a new medicine (... in England, the threshold recommended for non-exceptional cases is between £20,000 and £30,000 ...)..."

Then they say Scotland does not have an explicit threshold but in practice uses QALYs as a measure of value.

"Measuring value through an explicit cost-effectiveness threshold means that the drug requires an assessment of whether the additional health, measured mainly through QALYs, expected to be gained through its use exceeds the health forgone as other NHS treatments are displaced by its additional cost."

Now, this is the point I want to put to you:

"Since 1957, the government ... have set noncontractual agreements to ensure both access to medicines and fair returns for pharmaceutical companies, expressed as levels of sales ... [in]the [PPRS]. The PPRS explicitly mentions [value-based pricing] ...; for example, flexible pricing and patient access schemes can be used for adjusting the price of drugs whose incremental cost-effectiveness ratio is beyond the threshold ... or that exhibit different levels of effectiveness in real life ..."

Then the next paragraph:

"Health technology assessment authorities, and in

particular NICE, include the predicted effects of the PPRS in the final appraisal document, thus explicitly linking the cost for the NHS to the incremental cost effectiveness ratio-based assessment of value. Its explicit and relatively simple mechanism makes [value-based pricing] in the United Kingdom the most studied example ..."

Then two sentences on:

"The use of incremental cost-effectiveness ratio thresholds drive prices to levels consistent with the [willingness to pay] of the demand side ..."

Then:

"... adopting the health care and personal social services payer perspective in assessing the incremental cost-effectiveness ratio would lead to underestimating the value of treatment for disease areas in which the benefits affect significantly on non-health care and social costs, leading to underpricing."

So we can agree in the context of branded prescription medicines the concept of cost effectiveness as reflected in the QALY is directly hardwired into the PPRS system?

A. Can I ask what the expectations are for me here, because I have not read this journal article, I am very reluctant to comment on a journal article where I have

not read all of it, just because it is in a peer reviewed journal. As you will know, because you read journals yourselves, it does not necessarily mean you agree with it, it does not even necessarily mean it is true, so I am reluctant to comment on it.

THE PRESIDENT: That is entirely fair. I think either we need to invite Mr Hawkins to read the thing from end to end or you can ask whether from his own knowledge now he is able to agree, disagree or does not know, and I am happy with either course.

MR O'DONOGHUE: Well, Mr Hawkins, based on what I have shown you, is there anything you disagree with?

A. I do not have expertise in the PPRS. I don't feel comfortable commenting on it.

THE PRESIDENT: That is entirely fair enough, Mr Hawkins.

Mr O'Donoghue, do you want to press that?

MR O'DONOGHUE: Well, Mr Hawkins, you have been quick to make the point in your teach-in, and in your reports, that the NICE assessments do not affect pricing. What I am showing to you and putting to you is that in a branded prescription context -- and this is the point frankly, just made by Professor McGuire -- it is directly hardwired into that process that the cost effectiveness under the QALY and ICER thresholds is part of the pricing negotiation and settlement.

A. So NICE -- if you read through NICE documentation, we never mention value-based pricing. When the coalition government of 2010-2015 tried to bring in value-based pricing, tried to change the way that NICE worked, we immediately changed that to value-based assessment. If you ask NICE do you do value-based pricing we will say no.

It does not have a very -- from my understanding of it, it does not have a very exact definition, value-based pricing, but my understanding of it is it needs two elements: the first element is a clear list of criteria that links to a price that somebody is going to accept, and secondly, it needs a form of direct negotiation between the purchaser and the seller, and in my opinion, NICE does not have either of those.

Q. Can we look at what Professor McGuire says about this? This may be another way through this, if we go to {XE6/6/4}.

MS MORRISON: Sir, I do hesitate to interrupt, but just in terms of the question that has been put to Mr Hawkins, I would ask that he is allowed to read paragraph 17 of his witness statement because it seems to be being suggested that he said it has no relationship with pricing ever, and I think it would be fair to Mr Hawkins for him to refresh his memory of what he has actually

said on this topic.

MR O'DONOGHUE: Well, Ms Morrison -- I am very happy to do that, but Ms Morrison will have every opportunity to re-examine.

A. Is this 17 of statement 1?

THE PRESIDENT: It will come up, Mr Hawkins.

A. Oh, sorry.

MS MORRISON: It should be {XC1/6.1/5}.

THE PRESIDENT: Do you want to read that? (Pause)

MR O'DONOGHUE: Mr Hawkins, you do say there, at least in a TA context, that the QALY and ICER metrics are relevant to the negotiation of price. Do you agree with that?

A. I think I made it clear here I was talking outside my area of expertise. Since I have made this statement, I have read up more on patient access schemes, and I do not see it as -- if I could write this again, I would take out the negotiation part because the way these work is that the manufacturer recommends, let us just say, a discount on their list price, and then NICE say whether that is plausible or not to be given to the NHS, and that is then put through the technology appraisal process and then either a positive, negative recommendation is given.

There is not a negotiation in the same way there

would be a negotiation if you were buying a used car that somebody would say, you know, give me 12,000, I will give you 9,000 for it and then slowly meet towards the middle. If I was to write that again I would not use the word "negotiation", knowing more now than I did at the time I wrote that statement.

Q. So your evidence is untrue?

A. No, no.

THE PRESIDENT: Well, Mr O'Donoghue, I think we are at the fringes of where we were discussing the witness might end up a while ago which is he is here as a witness of fact. He has, I think, reached the limits where on this point he can assist the Tribunal. I am not going to permit the sort of cross-examination that you are going to launch upon at line 18 "so your evidence is untrue". I am taking the view that this witness is attempting to assist as well as he can the Tribunal in what is an extraordinarily complex economic and legal quagmire which, frankly, we are going to have to take some care to unpick ourselves and on which we have requested the assistance of the parties.

I appreciate that this is going to cause you some difficulties in the future questions that you have to ask this witness because you are expecting to get some answers on the record which are not "I do not know", but

I am saying now that I am not prepared to have the witness feel that he is being browbeaten. I know that is not your intention, but I am not going to have the witness feel that he is being browbeaten to give answers to questions which he does not feel able to respond to.

I meant exactly what I said earlier, Mr Hawkins, that from my point of view, and that is the one that matters, "I do not know" is a perfectly acceptable answer, and I will accept that answer, and Mr O'Donoghue will move on.

So I do not want to get into what you would have written if you had known more. It says what it says. If your answer to Mr O'Donoghue's questions is "I do not know", then do say that and we will move on.

A. Yes, understood.

THE PRESIDENT: Is that all right, Mr O'Donoghue?

MR O'DONOGHUE: Well, sir, that is perfectly fair, but you will understand from my perspective if things are included in a witness statement I cannot just glide over it. What I do not want it to be said in closings is X or Y was not challenged.

THE PRESIDENT: I quite appreciate that, and I think the CMA will appreciate from this dialogue that we are very conscious of the difficult position in which Mr Hawkins comes in trying to assist the Tribunal. The difficulty

is he is a witness of fact, a late joiner at NICE, and he is trying to help within those limits.

I have that point. I do not think that the CMA are going to be pressing on a point of controversy areas on which you have moved and asked where the response has been "I cannot help you because you have taken me beyond what I know".

MR O'DONOGHUE: Well, let me put one final question before we break -- I see the time.

THE PRESIDENT: Yes, of course.

MR O'DONOGHUE: If we can go to Professor McGuire's position paper, it is at {XE6/6/4}, Mr Hawkins you see there paragraph 12. Please read it. (Pause)

You will see Mr Hawkins in the middle he mentions the negotiation which is the point he just covered in the teach-in. Let me ask you this: do you disagree with what Professor McGuire says there or what he said in his teach-in just a moment ago, or is it simply outside your knowledge?

A. I would say TAs are outside of my knowledge. What I know on TAs is things I have read in the NICE guidance. I have no more insight than anybody else who has read those documents.

MR O'DONOGHUE: Fair enough.

THE PRESIDENT: Fair enough.

1 You think now is a good time?
2 MR O'DONOGHUE: Yes.
3 THE PRESIDENT: Very good. Do not talk about your evidence,
4 Mr Hawkins, while you are outside the box. I am sure
5 you would not want to anyway, but we will rise for
6 10 minutes and resume then. Thank you very much.
7 (3.37 pm)
8 (A short break)
9 (4.01 pm)
10 THE PRESIDENT: Mr O'Donoghue.
11 MR O'DONOGHUE: Mr Hawkins, go to your first witness
12 statement, {XC1/6/7}, please. There you will see,
13 Mr Hawkins, at 26, you see the heading "The 2012
14 Guidelines" and you have got, I count ten paragraphs on
15 the 2012 guidelines. Do you see that?
16 A. I can see that, yes.
17 Q. Now, I think we can agree that on the 2012 guidelines
18 you have no personal knowledge of those guidelines
19 beyond what you can read from the documents?
20 A. I did not work on those guidelines.
21 Q. I think the answer is yes, but for the avoidance of
22 doubt, if we look at paragraph 36 of your evidence
23 {XC1/6/9}, there is a dispute between you and
24 Professor Walker and you say in the last sentence:
25 "I cannot see that explanation given in the

guideline committee's reasoning ... in the 2012 guideline."

So I think this confirms my point. All you are doing there is reading the documents and saying, well, I cannot see that particular point?

A. That is correct.

Q. So, again, for the avoidance of doubt, no personal knowledge on this issue either?

A. That is correct, yes.

Q. Okay, so, Mr Hawkins, on that basis, I am not going to press you any further on the 2012 guidelines. If we can go back to paragraph 25 {XC1/6/7}, there you say:

"NICE does not inform the price of medicines, nor does it indicate or set prices."

And so on. Now, I think you said before the short adjournment that on reflection this is not something within your area of expertise?

A. I am not an expert on value-based pricing.

Q. Well, Mr Hawkins, on that basis, I am not going to press you any more on that particular issue. I will move on.

Now, what you do speak to later in the statement at 37 and following is the 2022 guidelines {XC1/6/9}.

I just want to ask you some questions about those to the extent of course you are able to help us.

Mr Hawkins, the starting point of course is that in the

2022 guidelines phenytoin sodium, as it was in 2012 and 2004, ultimately was recommended.

A. I have not looked up the 2004 guidelines; it was recommended in 2012.

Q. Now, you say at paragraph 40 of your statement -- it is on {XC1/6/10}, you say:

"Phenytoin was identified as a possible third-line ... treatment ... This is one line lower than recommended in the 2012 guideline."

Now, I would suggest to you that is not an entirely accurate way to characterise this. The guidelines distinguish monotherapy, adjunct therapy second-line, and tertiary, which is third-line, and in 2022, as it was in 2012, phenytoin sodium was a third-line treatment.

Do you agree with that?

A. That is not my understanding of it.

Q. Well, can we have a look at {XD1/6/1211}. You can see about two-thirds of the way down where it says:

"Phenobarbital, phenytoin, tiagabine and vigabatrin were recommended as third line add-on treatment based on the committee's opinion they can be effective treatments..."

So at least in 2022, phenytoin sodium was a third-line treatment?

A. I do not know where it is in my statement, but I think I make this point that we used slightly different terminology in the 2022 guideline to the 2012 guideline. When we talk about third-line here, we are talking about third-line add-on. My understanding is third-line in the 2012 guideline is one line of monotherapy and then your first-line add-on, what we are calling first-line add-on is what they are calling second-line, and what we are calling second-line add-on they are calling third-line. I do make that point somewhere in my statement. I do not know if somebody can get it up, or --

THE PRESIDENT: No, indeed. Mr O'Donoghue, could we get -- this is 2022, could we get the equivalent passage from 2012, because we are now on the fringes of something that is really more into the medical expertise in the sense that I understood both expert physicians to be saying that throughout its relevant history, sodium phenytoin was a third-line drug, and I do not think they were drawing any kind of fine distinctions between what third-line meant, and if that is their evidence, which I think it was, then with all respect to Mr Hawkins I think we are going to go with the doctors rather than with the NICE evaluation of what the doctors say.

MR O'DONOGHUE: I intend to move on on that basis.

Mr Hawkins made a point, I did not want it to be said that --

THE PRESIDENT: No, I do understand, but I think we need to be quite careful here about delimiting those areas where Mr Hawkins can assist and those areas where he is just going to be made uncomfortable because he cannot assist, and this is, I think, one area where we have had the best evidence that we are going to get, and, if anyone is objecting to this, then Mr O'Donoghue can move forward, but I do not see anyone rising on this.

MS MORRISON: Sir, I think the basic point is just simply that they divide things up separately. NICE did that, that was not done by the economic modelling and as you say, sir, the clinicians then explained that they agree it is third-line, so I do not really see there is any difficulty here.

THE PRESIDENT: There is no mileage in further questioning?

MS MORRISON: Yes.

THE PRESIDENT: Well, that is very helpful, Ms Morrison, thank you very much.

MR O'DONOGHUE: Sir, I will move on with that in mind.

THE PRESIDENT: I am very grateful.

MR O'DONOGHUE: Thank you.

Now, Mr Hawkins, a point you do make at paragraph 46 of your statement, and again, at 52 and 53

{XC1/6/10-12}, if you can quickly look at that, Mr Hawkins.

A. Sorry, which number again?

Q. It starts at 46 and also 52 and 53.

A. I think the second page is cutting off somewhat, I cannot ...

THE PRESIDENT: Yes, I do not think we have a complete page in either case, have we?

A. I can only read half of 46 at the moment.

THE PRESIDENT: If you jump over to the next page, 46 continues there, I think, Mr Hawkins.

A. It has changed now. (Pause) Yes, I have read the part of 51 that is on the screen now. (Pause)

THE PRESIDENT: We do not have the whole of 51, do we?

A. I have read the start.

THE PRESIDENT: You have read the start.

A. I am happy, I have read them.

THE PRESIDENT: I am grateful.

MR O'DONOGHUE: Now, Mr Hawkins, I am not going to go through any of the clinical evidence with you because that is not your area of expertise, but, as we saw in the guidance itself, go back to it {XD1/6/1211}, we saw this two minutes ago, the committee's ultimate conclusion is that phenytoin can be an effective treatment.

Now, by "effective", I assume you agree clinically effective at least, that was the committee's conclusion?

A. Yes, it would be unlikely that the committee would recommend ineffective interventions.

Q. Now, would it be fair to say that the cost effectiveness assumption or lack of cost effectiveness assumption, made in the 2022 guidelines concerning phenytoin, was ultimately overturned in the final committee's recommendation. The clear consensus was that the assumption of phenytoin sodium being as effective as a placebo was implicitly but clearly wrong, because that is why they said it can be an effective treatment.

Again, if it is outside your expertise, that is fine, but I am trying to at least understand where we disagree.

A. I think that is reasonable. I think it would be very, very unlikely that the committee would recommend an intervention that was not effective.

MR O'DONOGHUE: Thank you.

THE PRESIDENT: Mr O'Donoghue, Ms Morrison, I am wondering whether we ought to take the following course with the witness, but it is going to require both your buy-in.

It seems to me that in Mr Hawkins' evidence we have an extremely helpful pulling together of relevant material which goes to matters which we want to consider

for purposes of this appeal.

However, it does seem to me, given the answers that Mr Hawkins is very helpfully giving, that there is little additional material that he is providing out of his own mind, in other words, what we really are getting is a helpful collocation of materials which we ought to read but read on their own terms, and the extent to which Mr Hawkins is going to be saying: well, this is what NICE was doing at any one point in time is really not likely to add any value.

I mean, I am looking at his answer at the foot of page [180] where Mr Hawkins says, entirely fairly:

"I think that is reasonable. I think it would be very, very unlikely that the committee would recommend an intervention that was not effective."

Well, yes, indeed, but --

MS MORRISON: Sir, I think that was said in the witness statement anyway, that essentially you have the modelling process that the committee go on, so, as you are saying, there is not much that Mr Hawkins himself can personally add to: this is what I did and this is what the committee did, so, yes, I completely agree.

THE PRESIDENT: That is right, but the witness statement, to the extent it goes beyond what is contained in the documents that are contemporary at the time, is no more

than a helpful summary which we take just as that but with no additional weight because it is coming from the mouth of Mr Hawkins.

In other words, we will be looking at the documents that Mr Hawkins has very helpfully pulled together and, therefore, if we take that approach, we treat, if I can be as presumptuous as this, we treat Mr Hawkins as a glorified Civil Evidence Act notice and we read the documents because they are contemporary documents with that in mind, and you, each of you, make submissions on that basis, and no one on either side says: well, this is extra special true because Mr Hawkins says so or Mr O'Donoghue says: well, this has to be doubted because Mr Hawkins was cross-examined and denied it. We just have the documents.

MS MORRISON: To the extent that the statements just synthesise that which is there, it is because I do not know if you have had the joy of trying to read the whole of Mr Hawkins' exhibit to the statement but it runs to many thousands of pages. A huge proportion of the statements are just a synthesis.

To the extent there are other points that Mr Hawkins made that Mr O'Donoghue wants to question on, that is fine, but as you say, we will take the documents that NICE has read, we will be making submissions on those

rather than the synthesis in that sense.

THE PRESIDENT: Ms Morrison, the problem is the borderline between what is simply in the documents which we can read and what added value Mr Hawkins is delivering by way of his own factual recollection is precisely what Mr O'Donoghue is cross-examining on, and what I am saying is it is rather difficult for Mr O'Donoghue and indeed the Tribunal to discern what actually Mr Hawkins is doing beyond referring us to the helpful documents that he has exhibited.

Now, if that is the position and if the CMA are prepared to take that course, then we can take this rather more quickly, but if, on the other hand, there is stuff going beyond the documents referenced by Mr Hawkins that you are going to be relying upon later, then of course Mr O'Donoghue is going to have to carry on with his cross-examination.

That is what I am putting.

MS MORRISON: Sir, I think, so just thinking it through in terms of the documents, in large part they are just a synthesis. There are then points that Mr Hawkins makes that he believes are corrections to things that Dr Skedgel or Professor Walker have said that are signposted separately in the statement. To the extent that those are felt necessary to deal with here, I will

leave that to Mr O'Donoghue, but those sections of the statement are not properly described as a synthesis of what is in pre-existing NICE documents, so I cannot say that those are not things that we would rely on separately, but they are very limited.

THE PRESIDENT: So the corrections you would want to rely on?

MS MORRISON: Yes.

THE PRESIDENT: But Mr O'Donoghue, are you cross-examining on those?

MR O'DONOGHUE: Some, yes.

THE PRESIDENT: Some, okay.

MR O'DONOGHUE: Sir, that is extremely helpful and unfortunately the rather laborious process that we have been engaged in exposes the problem very clearly, but you will understand, sir, from my perspective I am on something of a horns of a dilemma.

THE PRESIDENT: I do understand.

MR O'DONOGHUE: Because it is being said in a somewhat amorphous way that there are a bunch of points which are unspecified that I need to take a view on whether I challenge and therefore, if I do not, it will be said against me that I did not.

So, sir, perhaps the way forward is the following: I have a handful of topics that I can put to Mr Hawkins

in terms of whether it is something he can assist us on. If the answer is no, we may have an early bath. If the answer is yes, he can, then I may need to pursue that further.

Let us see how much undergrowth I can clear out quickly.

THE PRESIDENT: That I think, Mr O'Donoghue, is very helpful, and let me be clear from where the Tribunal is coming from: we regard the evidence of Mr Hawkins as extremely helpful in terms of bringing to our attention and summarising the relevant contemporary documentation and we will look at it, in particular the parts that are referenced, but we would, I think take some persuading, particularly on a point of material significance, that if Mr Hawkins is saying something in his statement that is not in these documents or that is at variance with these documents, then we would want to tread extremely carefully and that is no criticism of Mr Hawkins, it is simply a reflection of the fact that he is primarily able to speak out of his own knowledge in respect of the 2022 process which was informed by the 2012 process and which he looked at for that purpose, but which otherwise he has no knowledge of.

Since we are not really that interested in 2022, we are interested in 2012 to 2016, which is where you

started, I hope you will take that as an indicator that you do not need to clear the undergrowth on the minor points, it will be very helpful on the major points if you identified whether Mr Hawkins feels he can assist beyond the documents, and then of course you must cross-examine, but if he says: it is in the documents and I have nothing material to add, then we can, as you say, take it more quickly.

MR O'DONOGHUE: Sir, yes, we have hundreds of pages of contemporaneous documents that we can read and make submissions on.

THE PRESIDENT: Well, I am not sure if that is a threat or promise, Mr O'Donoghue.

MR O'DONOGHUE: Sir, our job is to unpack them, but it is a bit of both, I am afraid.

So, sir, let me see how far I can go with the undergrowth.

So, Mr Hawkins, if we go to your second statement at {XC1/6.1/13}. Mr Hawkins, if I can ask you to read paragraph 44, please. (Pause)

A. I have read that.

Q. Now, Mr Hawkins, two questions which may be the beginning and end of this. First of all, if you look at the third sentence you say:

"This is most likely because of placebo drift."

So as I read that sentence, you are not saying that in the 2022 guidelines you and/or NICE actually took into account placebo drift in this context; is that correct? Because you use the words "most likely".

A. No, we adjusted the network meta analysis to account for differences in placebo response. The placebo response had changed over time in the placebo arm of the trials.

Q. So you are saying that NICE actually in this context adjusted phenytoin sodium for placebo drift?

A. For placebo response, yes.

Q. Well, I am afraid in that case I will need to ...

Now, my second question which again may be the end of this: you are not an expert in placebo drift, are you?

A. I consider it a medical term. The explanation given in the guideline document was written with help from the guideline committee. I am not an expert in placebo drift.

Q. Because the reason I ask of course is Dr Skedgel says he is not an expert in placebo drift and Professor McGuire does not touch on the concept of placebo drift, and you are not an expert in placebo drift either. That is not within your personal knowledge?

A. I feel like I have been backed into a corner a little bit here. It was the committee that brought up the

issue of placebo drift. The issue of placebo drift or placebo response, different placebo response over time, was brought up in the comments of the previous guideline, it was one of the -- of the 2012 guideline. It was one of the reasons the network meta analysis was dropped on that because of the criticisms of not doing that. That was not the only criticism of it. So the committee were keen that we looked at it this time, so I did that meta analysis at the start where we looked at the different -- sorry, it would be a lot easier if I could show my document, the evidence review F, but you will see at the start we did look whether placebo response had changed over time, this was at the request of the committee, so we looked at that, whether there was a placebo drift. We then adjusted for it in the network meta analysis, we compared the unadjusted model to the adjusted model, the adjusted model where we had adjusted for placebo drift, and that was a benefit, using the same criteria that Dr Skedgel uses for his measurement of model fit in his report.

So whilst I am not an expert in placebo drift, the guideline committee are, they asked me to look into it as a statistician, as a health economist, and that is what I did, but before I started this guideline I did not know what placebo drift was.

THE PRESIDENT: So the most you can say -- and do correct me if I am wrong, Mr Hawkins -- is that the committee was interested in placebo drift, they gave you some work to do which you did, you fed it back into the committee, but beyond that you cannot assist us any further because what the committee did or what it did not do is a matter for it and not for you?

A. Exactly. I mean, I can look at numbers and tell you if it is higher than 1 or lower than another, but we need that contextualisation of the medical experts and of the patient carer members. So, yes, I am not an expert in placebo drift, but I did look at it at the request of the committee.

THE PRESIDENT: Thank you.

MR O'DONOGHUE: Fair enough. I think, sir, in that case that is as far as I can take that particular point.

Now, A point you focused on in both of your statements and in the teach-in was the Cramer study.

A. Yes.

Q. I have a number of questions about that.

Now, if we go to your second statement at {XC1/6.1} at paragraph 43. It is just above where we have been looking. {XC1/6.1/13}. You are referring to Cramer. You say:

"Whilst this was a small trial and had a risk of

bias to it, it was the best evidence available for phenytoin in an add-on setting."

You had, I think, two slides in your teach-in on Cramer. Do you remember that?

A. Yes, I remember that.

Q. So from your perspective, this is an important piece of evidence?

A. It is such a loaded term "important piece of evidence". May I give a long answer?

Q. Sure.

A. So having to go back to the evidence that we have looked for, so we write a protocol with the committee asking them what evidence they want to look for in making their recommendations. The guideline committee then asked for double-blinded randomised control trials, they did not want to look at crossover trials, that is when somebody takes one drug for a certain period of time and then they will take a different drug for a certain period of time, then you will compare them before and after, they wanted them excluded out. That was their only inclusion/exclusion criteria in terms of trial design, there was no quality standard, there was no minimum number of participants.

So they asked to see all the RCT evidence that we found, and that is what we did. So in terms of that, it

is important because we are being systematic, the committee have asked to see this particular piece of evidence or piece of evidence that meet this criteria, and that is what I did, I presented this paper to the guideline committee and I put it in the network meta analysis as they asked.

Q. But you describe it in 43 as "the best evidence". What did you mean by that?

A. I think I said in my teach-in I used the word "best" here, it is the only evidence, I think either could be used there.

Q. Now, by contrast Dr Skedgel did not take into account Cramer because of his serious concerns about the limitations in that study; correct?

A. I don't recall. I thought he originally did not identify it and then he did not include it (a) because he was concerned about methodological concerns and (b) because he did not have a 50% reduction in seizure frequency in his model. That was my recollection, but I apologise if that is incorrect.

Q. Well, we can at least agree that he did not include it?

A. He did not include it, that is correct.

Q. Now, the Cramer study dates from 2001, and it was not referred to in the 2004 guidelines, for example. If you are not aware, that is fine.

A. Sorry, I missed the question. I have not reviewed the 2004 guidelines.
Q. The Cramer study dates from 2001; are you aware whether it was referred to in the 2004 guidelines?
A. It was not referred to in the 2004 guideline -- sorry, I do not know if it was referred to in the 2004 guideline, I do apologise.
Q. Fair enough. Now can we look at what NICE said about Cramer in 2012. It is at {XF3/73/94}.
You will see under 1 Cramer 2001 and you will see on the right-hand side it says:
"Very serious imprecision."
And then in the middle:
"Serious limitations."
A. Yes, I can see that.
Q. So in 2012, NICE, when they looked at Cramer --
A. Sorry, can I just confirm this is the appendix from the 2012 guideline, yes.
Q. This is appendix N to the 2012 guidelines.
A. Sorry, it has been a while since I have looked at some of these documents.
Q. Understood. So at least in 2012, NICE was saying about Cramer that it carries quite a health warning. Do you agree with that?
A. We say the same in 2022, that it has a high risk of

bias. We are not trying to claim it is a high quality randomised control trial but that --

Q. Well, I would suggest it is quite a bit more here. They say "very serious imprecision". Do you see that on the right?

A. Yes, I can see that.

Q. Now, let us just look at Cramer itself. It is at XF4, page --

THE PRESIDENT: Sorry, let us get paragraph 43 of Mr Hawkins' second statement back up. So {XC1/6.1/13}.

Now, do you have that, Mr Hawkins?

A. Sorry, which number? 43?

THE PRESIDENT: Paragraph 43 of your second statement which is at the top of the page on the right.

A. Yes.

THE PRESIDENT: So what you are doing here is you are explaining a difference in terms of what has been taken into account by NICE and by Dr Skedgel, and what you are discussing in this paragraph is that the Cramer et al trial was taken into account by one and not taken into account by the other. That is right, is it not? That is what you are commenting on here?

A. Yes. So the NICE 2022 model had the Cramer study in it, Dr Skedgel's expert report does not.

THE PRESIDENT: Does not.

A. Yes.
THE PRESIDENT: And what you are doing here in part is you are explaining why it was included in one and not included -- well, included in one, why it was taken into account by NICE.
A. Yes.
THE PRESIDENT: Are you making any implied criticism of Dr Skedgel's omission from his work of the Cramer et al trial?
A. Well, I would say this, the appendix document, if we go to table 2.15, I think it is from memory, {XF3/73/215}.
THE PRESIDENT: That is table --
A. It is essentially where we have evaluated the Bill randomised control trial from 1997 which is the one that Dr Skedgel extrapolates from, we have done the same for that trial within this appendix, if you can find that table I will show you where there seems to be an inconsistency in Dr Skedgel's reasoning. I think it is table 2.15. I do not know how that feeds into your numbering system.
THE PRESIDENT: Well, no, I mean, what I am trying to work out is what you are saying in paragraph 43 of your second statement that goes beyond simply identifying the difference between Dr Skedgel and NICE and explaining why NICE took it into account.

The question is whether you are going beyond that and you are saying that Dr Skedgel is wrong in omitting the Cramer et al trial and I think you were going so far as to say that that is what you are saying, in which case, Mr O'Donoghue will proceed.

A. Yes.

THE PRESIDENT: Yes, very good.

MR O'DONOGHUE: So to be clear, you are saying that Dr Skedgel's exclusion of Cramer should be criticised; correct?

A. Excluding it based only on its quality, I think that is wrong. If you accept that the two state model is the correct model which I do not, that would be a reason to exclude it because you are not looking for evidence for that, but excluding it on quality I believe is wrong, I believe it is unsystematic, I believe it goes against NICE processes.

Q. Okay, well let us --

A. And we do evaluate the Bill trial in this appendix if you can find it. You will see that that has similar, if not worse, quality rating than the Cramer trial, so where is the consistency there --

Q. Well, let us start by looking at Cramer, {XF4/32}.

A. I do want to make it clear I do not think it is a great trial. I am saying that the committee has asked to see

this trial. They are experts in their field, we have got consultants there, they can appraise the quality of the evidence, and they can deal with it appropriately. I am not at any point trying to claim this is a really, really good randomised control trial, I do not know if that is where this is leading.

THE PRESIDENT: Mr Hawkins, I think the reason I am asking questions about your paragraph 43 is simply this: I quite understand that different experts might take different views about what to include and what to exclude in their consideration, and if that is all you are saying, then we can, I suspect, move on rather quickly, but if you are going further and you are saying that there is something more than simply the difference of view, difference of judgment, between NICE on the one side and Dr Skedgel on the other, then that is something which we need to unpack, and your paragraph 43 does not say anything either which way. What it does is it explains why NICE took Cramer et al into account. It says nothing about Dr Skedgel except that he did not, and what I am reading from this is some kind of implied criticism that Dr Skedgel should have taken into account but did not, and if that is wrong, then we can move on, but if that is right, then we need to unpack your thinking.

A. That is correct, that was in response to saying that the NICE 2022 guideline was wrong to include it, and I think not including it is not systematic. Dr Skedgel has included other rather rubbish trials that scored lowly on quality, he has extrapolated from a trial that is reported badly in terms of quality, and I appreciate he had time pressures, so he has not done a full systematic review, but it was not clear from his expert report what his inclusion/exclusion criteria was for clinical trials. Was he excluding the rubbish trials, because he has included some rubbish trials, so that is the kind of the inconsistency with NICE processes that I am trying to point out in response to Dr Skedgel's criticism of my first witness statement.

THE PRESIDENT: Mr Hawkins, that is absolutely helpful, thank you very much. We will proceed on that basis, but thank you.

MR O'DONOGHUE: I think there is a hint of a criticism, if I can call it that.

Let me follow that up.

Now, if we can go to Cramer, it is at {XF4/32}, and if we can start at page {XF4/32/5}, please, under where it says "Conclusion". Now if you can read what is set out there, Mr Hawkins.

A. So I am reading the conclusion?

Q. Yes. (Pause)
A. It is a bit across a page. Can I go on to the next page? {XF4/32/6}. Thank you, I have read that.
Q. Now, a couple of points. If we go back to the previous page, I would suggest what is clear from that conclusion is that the Cramer study was not about the efficacy of phenytoin or indeed the AEDs they considered at all, but whether adding tiagabine to an existing regimen, including phenytoin, would affect the patient's quality of life, so it is about quality of life and not efficacy, because they say:

"... enhance patient perception of aspects of attention/concentration, memory, and language skills."

So it is quality of life, not efficacy. Do you agree with that?

A. I would agree that that is a fact that the primary outcome of this randomised clinical trial is this QOLIE-89 outcome.
Q. Now, insofar as Cramer touches indirectly on efficacy, if we can go to page {XF4/32/2} under "Results", please. Mr Hawkins, I am going to ask you to read the paragraph there under "Results".
A. The first paragraph?
Q. Yes. (Pause)
A. I have read that.

Q. Is it not clear from these figures that there is no material difference between the AEDs in terms of efficacy? It says:

"... did not differ significantly among the four treatment groups."

A. Yes, there was no statistically significant difference between the two treatments in this randomised control trial.

Q. Can we look at what Professor Walker says about Cramer, it is in his position paper. It is at {XE6/2} starting at page {XE6/2/13}.

It starts at 12.3 and then over the page. Mr Hawkins, if you can read 12.3 in its totality, please.

A. Sorry, 12.3?

Q. Yes. (Pause)

A. Sorry, go to the next page. {XE6/2/14} (Pause)

I have read it.

Q. So let me just put the propositions to you. One, he says it did not set out to measure efficacy and was about quality of life, I have already put that to you.

A. And I would agree with that, yes.

Q. Second, he says the study was not large enough to detect a difference in efficacy between the drugs or even to give reasonable confidence intervals for efficacy. Do

you agree with that?

A. That is true, but again, we are going back to this point of consistency. Dr Skedgel also had smaller trials than this in which also did not detect a difference for his main outcome, so there seems to be that inconsistency there, this is the point I am trying to make. If you exclude Cramer, if we should exclude Cramer there is other studies we should also exclude.

Q. That, no doubt, can be put to him.

A. Okay.

Q. I am asking you about Cramer. He says third:

"Little can be gleaned from this study, other than adding these drugs improved quality of life and seizure control."

Do you agree with that?

A. I am not going to give my personal opinion on this, but I think that is something that, if that is appropriate, that is something the guideline committee would do if there is little to take from it, they would take little from it.

Q. But you do not actually know that, that is your opinion?

A. Sorry, no, because that is how guideline committees are meant to act, they are meant to -- they ask us what evidence we want -- they want to see, we show it to them, and then they evaluate it, so that will be for

them to decide how much weight they want to put on that trial, it is not for me. I can explain the limitations with it, the risk of bias, it is for them to decide how much weight to put on that particular trial.

Q. Do you therefore accept you are not personally able to evaluate this study?

A. No, I do not have that medical background. That is --

Q. Now, to be fair to Professor Walker, he actually goes quite a bit further, he goes on fourth:

"... the evidence from this study would be considered ... very poor quality..."

And he says at the end:

"I am surprised that this study was included in any NICE (or other) analysis."

So Professor Walker's evidence which in fairness to you I should point out was not challenged in his cross-examination is that Cramer should not have been included in NICE 2022.

A. I would disagree with that.

Q. I would also put to you that on that basis Dr Skedgel acted more than reasonably in not including Cramer for the same reasons.

A. I would disagree with that. I think the only reason for excluding Cramer is that he did not put the greater than 50% reduction in seizure-freedom state in his model.

I think the other reasons he gives are not fair.

Q. Well, we disagree on that.

Now, a couple of final points of undergrowth. So again, you remember where we started. You were here as a factual witness to speak to matters within your personal knowledge. You remember the declaration you signed in the two witness statements?

A. Yes.

Q. Now, if we go back to your second witness statement at paragraph 42 {XC1/6.1/12}, you say, Mr Hawkins, in the second sentence:

"From my experience of working with guideline committees if they had accepted the outcomes of [Dr] Skedgel's analysis in their consideration of the cost effectiveness of ASMs, then phenytoin (and pregabalin) would have been recommended at a higher line of treatment than the other ASMs under consideration."

Now, you were careful to put this in conditional, hypothetical terms. Do you accept this is not factual evidence of which you have personal knowledge? You are positing a hypothetical? It is your opinion?

A. I am confused where the line is between fact and expert witness. I do not feel comfortable answering that.

Q. Well, do you accept it is at least an expression of your opinion and not a fact? You say "if". We know in fact

Dr Skedgel's model was not put to the committee. It is a hypothetical assessment. It is your opinion. Do you agree or disagree with that?

A. I answered that question -- well, I made that statement from my experience of working with committees.

THE PRESIDENT: Well, fair enough, but do you actually consider that you can predict what the guideline committee would have done if they had accepted the outcomes of Dr Skedgel's analysis?

A. So I have worked on tonnes and tonnes of guidelines.

THE PRESIDENT: Right.

A. If a committee is presented with strong evidence of effectiveness, as Dr Skedgel claims, strong evidence of cost effectiveness as Dr Skedgel claims from his expert report, then, yes, this is a cost effective drug, yes, it is an effective drug, it is going to improve health, I cannot see any reason why they would recommend other than for those drugs.

I think that is not opinion; that is a fact. I think anybody would come to that same conclusion.

MR O'DONOGHUE: Mr Hawkins, is it not apples and pears, because we have established that Dr Skedgel, we suggest for good reasons, for example, excluded Cramer, his analysis is simply based on a different corpus of evidence. You are not comparing like with like, and

1 therefore you cannot say as a fact that had the
2 committee been presented with this report they would
3 have done X, Y or Z. You simply do not know. You can
4 give your opinion, but in fact you do not know.
5 A. Well, I do not think anyone could predict a hypothetical
6 guideline committee with that degree of certainty.
7 Q. Well, that is my point.
8 A. I think with perfect certainty, but I think you would be
9 very, very, very certain that they would come to those
10 conclusions.
11 Q. We disagree.
12 THE PRESIDENT: Well, Mr Hawkins, let us move to a little
13 more granular. We know, for instance, that the Cramer
14 et al study is included in the NICE consideration and
15 excluded from Skedgel's analysis, we know that because
16 you have told us that. We therefore can say that the
17 weighting that Dr Skedgel gave to the Cramer study was
18 nil because he has taken it out of account, he has not
19 looked at it. You agree with that?
20 A. Yes, it seems --
21 THE PRESIDENT: Yes, it must follow?
22 A. Yes.
23 THE PRESIDENT: You also said a few minutes ago that whilst
24 Cramer would have been taken into account by the
25 guidelines committee, you could not say what weight they

would give to it. Do you remember saying that?

A. Yes, I remember saying that.

THE PRESIDENT: Right. So given that you do not know what weight the committee would have given to the Cramer trial, does it not follow from that -- and do correct me if I am wrong -- does it not follow from that that you cannot actually say how the committee would have assessed matters if they took into account the material that Dr Skedgel did take into account and that they did not because that is a question of their clinical judgment which you are not able to second-guess because it is outside your area of factual understanding?

A. I mean, again, I am not quite sure where the line is between fact and expert witness. I mean, everything that is in (inaudible) facts then you might as well just go to the guideline document. I think there is kind two of things here: one is we were talking about the Cramer trial earlier. If I remember this bit of the statement we are talking more generally about Dr Skedgel's work.

THE PRESIDENT: That is entirely true, and I am zoning in on one difference between the Skedgel consideration, which was to exclude Cramer, and the NICE approach which was to include it, but what you said was that inclusion did not say anything about weight, and so what I am probing with you is, given that that will be true about all of

the differences between Dr Skedgel's analysis and the NICE committee's analysis, it is all a question of weight and clinical judgment, what I am asking is how you can be so confident if it is a matter of judgment that the committee would have reached so dramatically a different conclusion that you are asserting in paragraph 42.

A. I do not think I am asserting there that the committee came to a dramatically different conclusion based on the Cramer trial.

THE PRESIDENT: What are you saying, then?

A. This is not -- if you could go back to the previous points, I am not discussing in particular the Cramer trial here. This is more the -- more the strong conclusions that Dr Skedgel has made around effectiveness and cost effectiveness, and I think it is truth, it is a fact, that if a committee found strong evidence of effectiveness and strong evidence of cost effectiveness they would recommend something.

THE PRESIDENT: Okay, so does it amount to no more than this, that if the committee 100% agreed with Dr Skedgel then they would 100% agree with Dr Skedgel?

A. I would not put it like that, but I am saying if you did believe -- as it says there, if you believe Dr Skedgel's analysis, you give it a lot of weight, then you would

follow those recommendations.

THE PRESIDENT: Thank you.

MR O'DONOGHUE: Sir, I see the time. I think I may have reached a terminus. Sir, with your permission what I would like to do overnight is -- I think either I have finished or I may at most need ten minutes in the morning. What I would like to do is triangulate the two statements and make sure I have put everything I need to put, because this has been slightly fluid, and in fairness to my client I think we need to double-check that we have dotted all the Is and crossed all the Ts.

THE PRESIDENT: That is fair enough, Mr O'Donoghue. My question is simply one of timing. Tomorrow is the last day for evidence. Are we going to be not squeezing anybody assuming a 10.00 to 5.00 day tomorrow?

MR O'DONOGHUE: Sir, as I said, it will either be nothing or ten --

THE PRESIDENT: No, I completely buy those ten minutes. I am interested in the two other witnesses that we are going to have to hear.

MR O'DONOGHUE: For my part, at the risk of further unpopularity, I would be content to start a bit earlier. On the timetable in principle we have half a day for each of the witnesses as scheduled --

THE PRESIDENT: Yes.

MR O'DONOGHUE: -- so we seem to be on track, but we have been saying that for many weeks, and it turns out not to be true.

THE PRESIDENT: We are more or less on track, and the reason you are not has been the interventions of the Tribunal, not the overrunning of counsel, so we are in a reasonably good state, but 5.00 is a hard deadline.

MS MORRISON: We also originally had 10.30 to 4.30 due to some considerations that were raised at the CMC on my behalf when I was not in attendance, so we actually both already have additional time by sitting 10.00 to 5.00. So from my point of view I cannot see any concern in a small runover in the morning. I do not think that is going to impact on us finishing tomorrow.

THE PRESIDENT: Very good.

MR O'DONOGHUE: Sir, if I can put it like this, if the CMA will endeavour to finish by lunchtime with Dr Skedgel, I will match that by undertaking to finish Professor McGuire by the end of the day.

THE PRESIDENT: Very good. Well, that is helpful. We can gain your 10 minutes by a minor encroachment into the short adjournment if you need it.

We will start, in that case, at 10.00 tomorrow morning. Thank you all very much.

Mr Hawkins, I am afraid you are going to be in what

we call purdah overnight. Please do not talk to anyone about your evidence. I am sure you would not want to, but have a good evening and we will see you tomorrow morning at 10.00, and it will not be very long. Thank you very much.

(4.57 pm)

(The hearing adjourned until 10.00 am on Friday, 1 December 2023)