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

Friday, 1 December 2023

(10.00 am)

THE PRESIDENT: Mr Hawkins.

MR JAMES HAWKINS (continued)

Cross-examination by MR O'DONOGHUE (continued)

THE PRESIDENT: Mr Hawkins, welcome back. Thank you so much for coming. Do sit down and we will see if there are any questions.

MR O'DONOGHUE: Sir, I have carefully reflected on Mr Hawkins' evidence overnight, I have been through his two statements in some detail. I think subject to one point everything I can deal with in submissions, so I have one short question.

Mr Hawkins, good morning.

A. Good morning.

Q. I am sorry, as a fellow weary commuter, to drag you in on a strike day for something brief subject to re-examination. As I indicated to the President, I have been through your two statements very carefully, and there is one point I want to round off. It is something we touched on yesterday, I think it can be brief and non-controversial, but you may tell me otherwise.

If we can go to your second statement, please, it is at {XC1/6.1/15}, Mr Hawkins, if you can look at the middle of paragraph 49, you say:

"The 2012 NICE epilepsy guideline considered time to withdrawal."

Then if you go down to paragraph 50 over the page {XC1/6.1/16} you will see in the second sentence and for the rest of that paragraph there is a further reference to the 2012 guidance, and you will see the start of paragraph 50, there is a debate between you and Professor Walker on a point concerning the 2012 guidance.

So my question relates to both of these paragraphs insofar as they refer to the 2012 guidance is the same as yesterday, which is you are not in a position, based on your personal knowledge, to speak to what was or was not taken into account in that guidance other than what you can read in the documents themselves?

A. That is correct.

Q. Now, one final point on this topic. If we can go to {Day6LH1/99:}, please. So this is Professor Walker's evidence. You will see, Mr Hawkins, at the top of the page, this is Professor Matthew Walker.

A. It is not displaying.

THE PRESIDENT: Ah right, can someone assist Mr Hawkins with his IT? Do not worry, Mr Hawkins, it is not your problem.

A. It has come up now. It has fixed itself.

THE PRESIDENT: Well, that is usually the way.

Right, do you want to give that reference again, Mr O'Donoghue?

MR O'DONOGHUE: Yes, it is Day 6 --

A. It has disappeared, I am afraid.

MR O'DONOGHUE: We start at page 98, please.

A. It might be better in paper form.

THE EPE OPERATOR: Has it disappeared again?

A. Yes, it has, I am afraid.

THE EPE OPERATOR: Has it just gone black?

A. It has just gone "network HD", like a logo.

THE EPE OPERATOR: I will take a look.

MR O'DONOGHUE: Sir, I have a hard copy if that is a temporary fix.

THE PRESIDENT: We may need that. Let us see. We have it back? Right, keep your hard copy ready, Mr O'Donoghue.

MR O'DONOGHUE: I have it on standby, sir.

Mr Hawkins, just for your benefit, if we can start at {Day6LH1/98:} just to see the context rather than jumping straight into the bit I want to focus on. If we look at the bottom of line 6, so start at line 16, there is a reference to the NICE guidance. If you can read the rest of that page, and then when you are ready, we can move to page {Day6LH1/99:} please. (Pause)

A. Next page, please.

Q. If you can just read to line {Day6LH1/99:7}, please.
A. (Pause) I have done that.
Q. The point I am putting to you -- and you may not be able to assist -- there is a debate between you and Professor Walker on the 2012 guidelines, you have accepted you were not directly involved in those. You see in lines 2 and 3 that Professor Walker did have a role in the context of commenting on the 2012 guidance, and do you accept that he is better placed than you are, therefore, to comment on this aspect of the guidelines?
A. What he has done here is he has responded as a stakeholder. Anyone can respond as a stakeholder to a NICE guideline. If you are a registered stakeholder then you will get a response from NICE who will write a comment back to you. If you are not a registered stakeholder, you do not get a reply, but your comment is still taken into account. So that is how, from my understanding of this, that is how Professor Walker has fed into the process.

Those comments are online, they are published, so whatever comment Professor Walker sent in, that will be readily available on the NICE -- on NICE's website. I read the comments on the previous guideline, especially around focal epilepsy, so I do not recall it

now, but I potentially read that, so we have all got sight of the same comments that have been submitted, so he might be better placed in terms of his expertise to comment on it, I will leave that for others to decide, but in terms of having extra information, I would have to disagree.

MR O'DONOGHUE: Thank you, Mr Hawkins.

Sir, I have no further questions.

THE PRESIDENT: Thank you very much.

Ms Morrison, any re-examination?

Re-examination by MS MORRISON

MS MORRISON: Mr Hawkins, you will be happy to know I only have two re-examination questions. One is just a clarification.

You were asked about -- the question was put to you: "Question: ... you have only worked at NICE for, I think, about 18 months; is that correct?"

And you said yes. I just wanted to ask was that you coming new to the work of NICE 18 months ago, or have you been involved for longer?

A. No, I have been involved in the process of NICE guidelines, I have produced the NICE guidelines for -- it is over ten years now I think, I will have to go back and check my LinkedIn, but it is around about ten years.

Previous to that, I was -- I was previously at two externally funded -- sorry, NICE-funded external collaborating centres which NICE fund to -- or used to fund to produce their guidelines.

I might get the exact years wrong, but six years of that I was at the Royal Obs and Gynae where the National Guideline Alliance was hosted, that is where I produced the epilepsy guideline, and previous to that, I was at the Velindre NHS Trust as part of the National Collaborating Centre for Cancer, so I have worked with NICE, I have communicated with NICE for much longer than that.

Q. I hope, you mentioned a couple of times in the document {XF3/73} that you wanted to show the Tribunal something about Bill et al. You were shown a different page about Cramer. I think I have found the page, but let us see. If we could go to {XF3/73/12}, please. Was that the table you were looking for at the bottom? You were discussing with Mr O'Donoghue the Cramer trial, and he showed you the table on the Cramer trial, and you mentioned a couple of times that there was a table in here that dealt with the Bill --

A. I think it was table 2-5.

Q. 2-5, okay, well we did not -- could we run forward to find 2-5, please?

THE PRESIDENT: Flick through the pages and we will see when 2-5 comes up.

A. I hope I have remembered that number right or the wrong table is going to come up.

THE PRESIDENT: If you see it on the way, do shout.

A. It is not scrolling on my screen so.

I think there are hundreds of tables unfortunately.

MR O'DONOGHUE: If it helps, we can tender this (inaudible).

THE PRESIDENT: That is helpful. We will give it another -- we are almost there.

A. There we are, excellent. {XD3/73/126}

So I was trying to refer to this when I was trying o talk about systematic reviews, why we put the Cramer trial in. So we set our inclusion criteria, in this case it was double blinded randomised control trials, our population, our intervention, comparator, our outcomes, and we set that before we start looking for the evidence and then we search for evidence based on that, include/exclude trials based on that, and that is the evidence presented to the committee.

The importance of doing that, setting that beforehand, making those decisions beforehand rather than making those decisions afterwards is that it reduces bias out of the equation. You cannot eliminate studies you do not like and include studies that you do

like.

So, for example, if you are doing a technology appraisal and you are reviewing the previous evidence for your -- for the drugs that you had as comparators and then you see, you get, let us say for example you get five randomised control trials, if you wanted to -- there may be two trials in there with a younger population that have better results. If you wanted to improve your offering, you might want to get rid of those two trials, so the effective assessment of your comparators goes down.

So you could then just spuriously afterwards just say: actually we are going to eliminate these two trials based on these reasons and if you have not listed them beforehand, there is some bias there.

So I think -- the thing I was trying to say with Cramer, it may have been a post-hoc decision made there to eliminate it based that it is not a very good trial so that is why I wanted to compare it with Bill, the 1997 trial, this is the study that Dr Skedgel extrapolates from, and just to compare the limitations of that study to the Cramer study, and there seems -- to me there seems to be an inconsistency there that you would eliminate Cramer because it is not good quality but look at this: serious limitations, serious

indirectness, very serious imprecision again, but you would not eliminate this. In fact, this is the key driver of all the results of Dr Skedgel's model, there seems an inconsistency there to me.

THE PRESIDENT: Anything more, Ms Morrison?

MS MORRISON: No, thank you, sir. That is everything from me.

THE PRESIDENT: Mr Hawkins, thank you very much. I know you have come a long way to give evidence for a short period of time this morning, so it is with our particular thanks that you leave the witness box, but you are released from the witness box. Thank you very much.

THE WITNESS: Thank you.

MR O'DONOGHUE: Dr Skedgel.

THE PRESIDENT: Dr Skedgel.

DR CHRISTOPHER SKEDGEL (recalled)

THE PRESIDENT: Dr Skedgel, good morning. Do be seated. Make yourself comfortable. You have water and a glass there. You will be proceeding straight into cross-examination because you are still under oath and your reports have been adduced into the record, so you will get some questions from Ms Morrison.

Cross-examination by MS MORRISON

MS MORRISON: I do not know if first Dr Skedgel wants to find his own expert reports and things. I think you

have Mr Hawkins' statements in front of you --

A. I do.

Q. -- so if you want to orientate yourself first, please.

(Pause)

Good morning, Dr Skedgel. I have a number of topics to discuss with you today. My aim is to clearly signpost what I am focusing on at all times, but please do say if you need some clarification of what we are focusing on and so forth.

I do appreciate it is difficult to take on the spot exactly what someone is saying to you, process it and answer, so please, just at any point ask for clarification or a repeat of anything I have asked.

We will go to some of the documents today. I think most of them, or indeed most of them, certainly, you have already seen before. They either originated from Pfizer or you referred to them in your documentation or they were part of the trial bundle, but please, at any point, if it is something that you are not familiar with, please do indicate if you need some more time to read it, to read a wider passage and so on.

The last thing I will say by way of introduction is, as you may be able to hear, I have something of a horrible cold. If I cough or screech or anything else, it is not a tactic, it is just the never-ending

cold.

So moving to our first topic, I would like to start by clarifying the scope of your instructions so that I can be very clear exactly what I can and cannot discuss with you this morning, and so that we do not get into any difficulties or at cross-purposes.

So could we go first to paragraph 18 of your first report. It is at {XE3/1/5}. To orient us, you have just explained what you have done in your economic model and you say:

"Of course, this does not mean that the NHS will always pay prices equal to those that meet NICE's value-for-money test. Competition can play a role in driving down prices so giving the NHS better value-for-money. Discussion of the role of competition is not, however, part of my remit, and I do not discuss this further."

The first thing I take from this is that you accept that the NHS does not necessarily pay the price at which the treatment passes the QALY test?

A. I accept that, yes.

Q. And to confirm, you do recognise that competition therefore plays a role in driving down prices, so in terms of determining what actually is paid by the NHS?

A. That is correct.

Q. Given your expertise in this area, Dr Skedgel, I just want to check, I am sure you are aware that the Department of Health relies on competition to control the prices of unbranded generics?
A. I understand that, yes.
Q. And there are, of course, other policy levers used by the department such as the PPRS?
A. That is correct.
Q. But you have not been asked to consider the role of competition or any of these policy levers as part of your analysis?
A. I have not been asked and I would not consider myself an expert in those areas.
Q. Thank you, Dr Skedgel. It is really helpful just to clarify. I also do not believe that you have been asked to consider the implications of where a drug sits in its lifecycle as part of your analysis?
A. I have not been asked specifically to consider that, no.
Q. So I do not believe that you make any distinction in your reports between drugs that are patented, branded and unbranded when you are discussing, so for example the pricing of drugs?
A. No, indeed, as I recall, I think I make the point that I am agnostic about the point (inaudible).
Q. Can I just be very clear: I do not believe you have

considered in your discussion of the Flynn supply price, so your primary analysis where you discuss the just over £60 price, I do not believe that you have actually considered whether or not the NHS would have been reasonably willing to pay that price under competitive conditions. That is not something that you have been asked to consider as a health economist?

A. I think I have a difficult time separating what I think -- sorry, if I can say the question back to make sure that I understand it?

Q. Of course.

A. I do not think I am making any conclusion or judgment about what the NHS would have paid in this particular case, only I am analysing value in a health economic approach, relative to what NICE uses as its threshold. So I think there might be some grey area between the general principle of what NHS considers reasonable value and what they may have paid in this particular instance.

Q. Dr Skedgel, we will come back and discuss the relationship because it is one of the points I want to discuss with you later, but just to clarify for now, my understanding is you have been instructed, essentially, that the economic value test the Tribunal is applying is a legal one, so it is not for you to consider; is that right?

A. Correct, yes.
Q. So just to confirm, you do not reference it in any of your reports or your position paper, because it postdated it, the previous judgment of the Tribunal in the *Hydrocortisone* case where it discussed things like consumer surplus, you have not considered any of them?
A. No.
Q. My second very brief topic focuses on the facts, essentially phenytoin's history itself as a drug and its assessment by NICE previously. Are you aware, Dr Skedgel, that phenytoin was first synthesised in 1908 and first commercialised in 1938; were you aware of that?
A. I am not sure that I am 100% aware of the precise dates, but I am aware that it is a very old medicine.
Q. We can agree that. It went off-patent long before Pfizer actually acquired phenytoin in 2000, so it has been off-patent for some time?
A. I can accept that.
Q. Did you know that phenytoin used to be sold as a branded product, Epanutin?
A. I am aware of that branding.
Q. But as part of the arrangements that are at issue in these proceedings, phenytoin became an unbranded generic drug. You are aware of that?

A. I am aware of that.
Q. So would you agree -- I know you have not been asked to consider it, but just to check if you would agree with it, the capsules at that point, in the 2012 to 2016 period were in the third stage of the drug lifecycle; is that right?
A. I cannot say that I was specifically aware of what stage they were at in 2012.
Q. That is fine, Dr Skedgel. It just helps if I find out what building blocks we agree on, it helps with the questioning later on.

Phenytoin has been the subject of consideration by NICE on three occasions: first in 2004, are you aware of that?
A. Aware of that, yes.
Q. Second in 2012, which is the report that was right before the relevant period?
A. I am aware of that, yes.
Q. And third in 2022, which is the report that you note post-dates it, there has been a lot of debate about in these proceedings?
A. I am aware of that one, yes.
Q. On all three occasions, this evaluation was completed in the context of NICE promulgating guidelines, was it not, it was always about guidelines?

A. Correct, yes.
Q. So phenytoin has never in fact been the subject of a technology appraisal by NICE?
A. Not to my knowledge, no.
Q. As a consequence of the fact that phenytoin has never been the subject of a technology appraisal, phenytoin has never also been the subject of the statutory requirement for the NHS to fund it?
A. Also not to my knowledge, correct.
Q. Now, I just want to check if you have seen something that I have not. So I have reviewed your reports very carefully, as you can imagine, but correct me if I am wrong: you do not refer to any documents showing that Pfizer or Flynn conducted their own QALY analysis in 2012 before introducing the price increases?
A. That is correct, I am not aware of that analysis.
Q. You have not seen anything like that? Nor have I. Or that they carried out any such analysis during the relevant period up to 2016?
A. Not that I am aware of.
Q. Or that anyone such as yourself was appointed before the start of these proceedings to do a QALY analysis?
A. I have no knowledge of that.
Q. I would like to move now to my third topic, which are real basics, I just want to cover some of the ground

again and see where we are agreeing, and so I believe quite a lot of this is common ground, so hopefully we can whip through it fairly quickly.

So I believe that NICE's approach analyses the cost effectiveness of a drug relevant to available alternatives?

A. That is correct, including a -- yes, as we discussed yesterday (inaudible).

THE PRESIDENT: Can you move a little closer and move the microphone a little nearer and we will see how we proceed.

MS MORRISON: It might actually help, Dr Skedgel, if I move this way a bit because I think what is happening is he is turning to listen to me and he is turning away from the microphone so I will just move up slightly just to make it a little bit easier for him.

THE PRESIDENT: Thank you very much, Ms Morrison, much obliged.

MS MORRISON: So QALY is always carried out by reference to a comparator and that is usually the current standard treatment?

A. Correct.

Q. So in the NICE 2022 analysis, the reference comparator was carbamazepine?

A. The comparator will depend on -- I think as I mention in

my teach-in yesterday, the comparator is not so much defined a priori as it emerges from the analysis itself, it is whichever is the least costly alternative among the comparators.

Q. There is essentially -- for epileptic treatment, the way it is being done by both yourself and NICE, so far as I understand it, is that you end up with a reference product and you use that.

A. Correct, yes.

Q. So for NICE it was carbamazepine, for you it was pregabalin, but I understand it should make no difference, ultimately, to the results, in a sense?

A. Broadly speaking, I think that is correct, yes.

Q. You mention now, and you mentioned yesterday that there can be a sort of no treatment, by which I mean I do not think the NHS ignores patients, there will still be GP appointments and things?

A. Correct.

Q. But in the epilepsy field, it has always been done to one of the very many anti-seizure medications that is available.

A. To an active comparator, yes.

Q. An active comparator. So again this is covering some ground from yesterday, but just to get it briefly, as has been discussed in the teach-ins, NICE conducts QALY

analyses in two particular contexts, first, the guidelines context, which is when phenytoin has been considered previously?

A. Correct.

Q. And second, in the context of technology appraisals?

A. Correct.

Q. Now, these technology appraisals I think we do agree are at least mainly carried out in respect of new technologies?

A. Mainly, yes.

Q. And technology appraisals can also be carried out for new indications of drugs when there is something new?

A. Correct.

Q. Can we go to your teach-in slide from yesterday, slide 12, which is at {XE7/8/12}, just so that you have it in front of you, it is the middle bullet point, just to read it out:

"The Technology Assessment ... programme assesses value of a technology relative to one or more comparators. TAs typically focus on the newest (and most costly) technologies, but there is nothing in NICE guidance or methods that prevent the assessment of older technologies. Indeed, many of the comparators in any TA will be older (generic) technologies."

Can we just break this down a little bit?

I think everyone agrees that the comparator used, the reference product, could be an older generic technology, I think you agree with that as well, that is what you say?

A. Yes.

Q. But in those circumstances, it would be the newer treatment which would be the focus of the analysis?

A. Correct, but from my perspective the focus of the analysis does not change how these items are incorporated into the assessment.

When you are conducting an assessment, there is nothing, again, in the methods that says: I treat this slightly differently in my model because it is the focus or the primary interest. Again, everything just sort of emerges from the model.

Q. You are looking at it from the point of view of the health economist about what happens in the model, but in terms of the real world, if the generic drug is just used as a comparator, it would not be the subject of the statutory requirement to fund it, so the consequences are different?

A. Yes, I think that is fair to say.

Q. If the comparator is in the guidelines, I have seen no indication that whatever happens in the technology appraisal then feeds into the guideline process in terms

of the generic, it does not change that drug's status, for example, third line or second line?

A. I do not think I am qualified to comment on how NICE would treat the results from a generic in a TA in a guideline.

Q. Unless I have missed it, I do not think you have identified any example of an unbranded generic being the subject, so the product that is being considered as the main product in a technology appraisal?

A. Correct, not that I am specifically aware.

Q. Can we go to paragraph 47 of your position paper, please. Actually, no, we do not need to go there, never mind. Sorry, that is Skedgel. I think we have already answered that.

So now moving to what NICE does when it calculates QALYs and ICERs, it analyses effectively an opportunity cost; is that right?

A. I think part of the discussion in the teach-ins yesterday was it is not quite clear what NICE is assessing their value of a QALY on the basis of. There is some school of thought that it is opportunity cost, there is another school of thought that it is some version of societal willingness-to-pay, so I do not think I am ready to say that it is absolutely opportunity cost.

Q. But in very simple terms -- and this is just talking about an aspect of what NICE does -- what Mr Hawkins has explained is what they are concerned about is we are taking £20,000 away from somewhere else in the NHS to fund the drug under consideration, so you want to at least get -- figure out whether you get an additional QALY, so insofar as that very simple -- sorry, I should have clarified -- that very simple aspect of the process, that is essentially trying to do some realm of an opportunity cost analysis?

A. Yes, opportunity cost in the sense of efficiency and maximising health gains within a budget, I would accept that, yes.

Q. Just to confirm, the QALY analysis looks at total treatment costs, not just the price of the drug. We tend to talk about this as focusing on the drugs, but of course it is the wider treatment?

A. That is correct.

Q. The price of the drug is just an input into the QALY analysis: it is set by the manufacturer and NICE takes the price as a given?

A. NICE -- correct, NICE does not intervene to set the price of a medicine, but, again, as I think I covered in my teach-in, my position is that there is an indirect influence on price, yes.

Q. We will certainly come on to talk about value-based pricing. I think that is one of the points you make, is just that it is an input, so I just wanted to confirm that today.

A. Yes.

Q. NICE may also consider other factors than just the ICER result, it is not determinative?

A. That is correct.

Q. We will discuss the thresholds in much more detail, as I am sure you will be delighted to hear, momentarily, but you have explained in your evidence that if in particular the ICER is greater than 20,000, NICE can consider uncertainty around the ICER any uncaptured or non-health benefits associated with the technology, equity issues and wider costs and benefits to the NHS and society. Is that right?

A. Yes, I think you are perhaps reading from the NICE methodology guideline which I am aware of, yes.

Q. I think it is actually a quote from you, but I think it is a quote you have taken from the NICE guidelines, so we are all regurgitating NICE's literature.

Can we go to Mr Hawkins' first statement on this at paragraphs 22 to 23 which is at {XC1/6/6}. Could I ask everyone to read paragraphs 22 and 23. (Pause)

The first point to take from that is that

uncertainty is equally important in the context of guidelines, we tend to focus on technology appraisals, but it is equally important in the context of guidelines.

A. Based on my understanding of guidelines, I am not sure I would accept that statement. One of the distinguishing features of the guidelines process compared to the TA process is guidelines are much more pragmatic, and in that sense, I think they are more open to a bit of uncertainty than perhaps a TA process would be, so I am not sure I would strictly accept that it is equally important.

Q. We will come back to that in a moment. Just focusing now on the first point in paragraph 22, the first Roman numeral:

"(i) the degree of uncertainty around the ICER ..."

And it becomes more cautious about recommending a technology.

"...(... when advisory bodies are less certain about the ICERs presented in the cost effectiveness analysis) ..."

Would I be right to say that NICE is concerned with decision uncertainty and is concerned with the probability that a different decision could be reached if the true cost effectiveness of each technology could

be ascertained before making the decision?

A. I think it is true that NICE does take uncertainty into account in their decision-making, yes.

Q. Can we go to your second report which is at {XE3/2/16} and start with paragraph 43 which is at the very bottom of the page and goes over the page. If I could just ask everybody to read paragraphs 43 and 44.

THE PRESIDENT: Would it be possible to have both pages side by side? Thank you. (Pause)

MS MORRISON: In paragraph 43 I think you were referring to the Claxton paper that you were also discussing yesterday in your slides, which is about the economic theory that investment decisions should be based on the expected value of the decision parameters?

A. That is correct, it is not the exact same paper, but the book that I cite here cites that paper, so --

Q. Right, I see, and in a sense, that is the approach you took in your first report of focusing on the expected value?

A. Correct.

Q. But I think then what you are acknowledging in paragraph 44 is that is not the way NICE approaches things, so they see value in technologies -- see less value in technologies that have greater uncertainty and that is a point you explain, that:

"... given two medicines with the same expected costs and outcomes, that where one medicine had more uncertainty around those expected values, NICE would tend to see less value in the more uncertain alternative relative to the more certain alternative."

So it is fair to say that uncertainty is pretty central to NICE's decision-making?

A. Yes, and here I think it is important to distinguish I was trying to estimate the expected cost per QALY gained, which to me is different, as I think you have appropriately pointed out, is an important factor in NICE's decision but not, as you say, deterministic.

I have tried to focus on the estimate and tried to avoid making any implication of what the decision would have been. So I would see uncertainty relating to the decision but not necessarily to the estimate itself.

Q. So I take it you agree, based on that answer, which is very helpful, that what Mr Hawkins said yesterday about NICE being a risk-averse decision-maker, you accept that?

A. I accept that, yes.

Q. You did outline yesterday your position on this expected value approach, and that is your approach as a health economist, but I am correct to say in light of the answers that you have given that NICE does not adopt

that expected value economic theory in its approach to its decision-making?

A. I do not think I would say it does not adopt, but it adopts, perhaps you could call it, a hybrid version where pure economic theory might, say, make the decision on the basis of expected value, they make some hybrid decision based on a combination of the expected value and the uncertainty, but again, like lots of things in the NICE process they have never specifically said how much weight they give to one or the other factor in their decision.

Q. So NICE would look at, for example, the outcome of a probabilistic sensitivity analysis to decide how much confidence it has in the results that have been put forward for it to consider?

A. Yes, that is correct.

Q. Now I want to focus on what NICE does not do as part of the QALY analysis, and I think it slightly maps on to what you have therefore not done in your report that we discussed earlier, but just to make sure we are all very clear. QALY analysis does not take directly into account the age of the technology, I think you say that in paragraph 4.1 of your first report?

A. I accept that I would have said something like that, yes.

Q. I think you also said it does not take into account the place of the drug in its lifecycle?
A. Correct.
Q. I think you said it was agnostic, you were agnostic, NICE is agnostic, for QALY analysis?
A. That is correct, yes.
Q. So again, in the QALY analysis itself it does not take into account whether the relevant drug is patented or branded, it is not making any distinctions on that basis?
A. Correct, correct.
Q. I think you have also explained -- I do not need to turn it up, but if you do need to see it at any point do say -- you said in paragraph 23 of your second report:

"... NICE has never referenced production costs in its assessments. Quite simply, the costs of production of a particular manufacturer, or its actual or potential competitors, are not relevant to NICE's assessment of value at a price set by the manufacturer."

So to the extent that the Tribunal considers that it has to take into account some things such as the manufacturer's costs, QALY analysis is not going to help it on that front?
A. That is correct, like I say, I have never seen anything about cost of production in a NICE assessment.

Q. Now I just want to quickly clarify just the process adopted by NICE, I think this is again set out in your evidence, but just to go through it. So for technology appraisals, the manufacturer will submit a value dossier for the product which includes an economic model, like the one that you have produced for phenytoin in this appeal?

A. That is correct.

Q. The Evidence Review Group or Expert Review Group, whichever name it was at the time, will then critique the submission and may make changes to the model?

A. That is correct.

Q. Now, of course, that has not happened in respect of your report, that is not a criticism, it is just a fact.

A. That is correct.

Q. You said in your position paper that the changes made by the ERG reflect normally their view of a more plausible and technically more conservative estimate of the value of the technology, so NICE normally revises things down rather than up, is that right?

A. That is typical I would say, yes.

Q. So then the NICE appraisal committee would receive the original dossier and the ERG's critique and the committee then decides what it thinks the most plausible estimate is to inform their final decision?

A. Yes, correct.
Q. And again, no criticism, but that has not happened here, there has been no input of that kind?
A. Correct.
Q. You also explained in your second report that the HTA process often involves resolving differences between the views and conclusions of the manufacturer and ERG in relation to methods, results and values. There is often disagreements?
A. There is often disagreements, yes.
Q. Again, that process has not occurred?
A. Correct.
Q. Do you accept, Dr Skedgel, that if you submitted your analysis to NICE, the most likely result would therefore be changes that revised your estimates upwards rather than downwards?
A. To the extent that there were any changes, yes, I would expect that they would be in a more conservative direction.
Q. You will be delighted to hear that my fourth topic I am moving on to now is the threshold. I had not realised how much information there could be on a threshold, but anyway. The issue I really want to discuss with you is to what extent the thresholds can guide an understanding of what the NHS is reasonably willing to pay but taking

very much on board the indicators you have given as to the scope of your instructions, so if at any point this is just not a question for you, please do just say.

A. Thank you.

Q. I am going to start with the easy basics for us and ease us in.

Starting with what the thresholds are. Mr Hawkins has explained that NICE applies different thresholds as a guide in respect of the two processes that we are talking about, so for technology appraisals the threshold range is of £20,000 to £30,000. You have mentioned it in your reports, everyone has, that is right?

A. That is correct.

Q. But Mr Hawkins explains that for guidelines, the guide threshold is lower at £20,000; do you accept that?

A. I accept that, yes.

Q. So pausing there, just to orient us in terms of what that means for your analysis, as you outlined in your reports and in your teach-in, your primary QALY analysis, which is the price that was paid by the NHS at the beginning of the relevant period, your analysis suggests that phenytoin would have an ICER of £19,557?

A. That is correct.

Q. So that would be just inside the guidelines threshold?

A. Just within, yes.
Q. And it would be just within the lower end of the range for NICE, for technology appraisals, of £20,000 to £30,000?
A. I think it would be just -- depending on how you want to phrase it, it would be just below what they consider an acceptable range. Below in the good sense.
Q. I think it is fair for me to show you the manual rather than try and read lots of bits of it to you, just to make sure we understand how the TA different levels work. So if we could go to {XF3/58/171}. If I could ask everyone to read -- I am sorry, this is a lot of reading -- but 6.3.4 through to 6.3.7, please.
Could we go over the page to 6.3.7 so you could read through {XF3/58/172}. (Pause)
Just on 6.3.4, it is right that NICE says that a technology will normally -- and I stress normally -- pass only if its ICER cost per QALY is below £20,000, it does not guarantee, it does it?
A. That is correct.
Q. Mr Hawkins says in the context of guidelines if the intervention is near to or at the £20,000 level, NICE usually requires more certain evidence around the treatment's effectiveness and costs. Do you accept that?

A. I can accept that, yes.
Q. Mr Hawkins also explains the higher threshold range applied in the technology appraisal context is generally to account for the innovative nature of the technology. Would you agree with that?
A. Innovation is one factor, equity factors can be another. There are specific distributional equality goals that the NHS and NICE pursue, but, yes, in general.
Q. So taking the wider factors as well, I appreciate innovation is just one of them, but it would suggest that for the purposes of technology appraisals, the higher threshold implies that NICE places some additional value on new technologies and new innovations?
A. Yes, I think that is fair to say, yes.
Q. So the fact the drug is patented has at least an indirect relevance to how NICE approaches its overall assessment of the drug, because it tends to be new drugs are patented drugs?
A. I am sorry, could you repeat that question?
Q. I am sorry. So we have discussed the fact that patented drugs, whether they are patented or not, is not something that is taken into account in the QALY analysis itself, but in setting the threshold, NICE applies a higher threshold for newer technologies that

takes into account innovation, I think Mr Hawkins referred to it as innovation premium.

So do you accept that the fact a drug is patented so it is a new technology has at least an indirect relevance to how NICE approaches its overall assessment of the drug?

A. I think to some extent I think might be getting the direction of causality wrong. I agree with you that NICE will tend to apply more value to an innovative drug and to the extent that innovative drugs are more likely to be new and therefore patented I can accept that argument, but I do not think it starts from the point that the drug is patented.

Q. I believe you agree that NICE does not apply an absolute or a hard-edged threshold to distinguish cost-effective treatments?

A. I would agree, yes.

Q. I think you accepted it was more of a rule of thumb, I think that is the language that you used yesterday?

A. I did use that language, yes.

Q. I think we have aired NICE's dirty secrets when it comes to their threshold. So I think that means that a treatment may still be recommended if it exceeds the threshold?

A. That is my understanding, and, as I think I presented in

my teach-in, there is our academic studies that try and put a number on that, yes.

Q. I think Mr Hawkins said that they vary wildly from finding it is 5,000 up to 70,000, which is also helpful.

A. I think we were speaking in different contexts, but, yes, I can accept that.

Q. So a treatment may still be rejected even if it is most plausible estimate gives rise to a cost per QALY below the £20,000 guide threshold?

A. It is rare, but it is possible, yes.

Q. Could we go to a paper called Dakin et al. It is at {XF3/36} and I would like to go to page {XF3/36/10}.

I would like to focus on the figure at the top of the page, so as big as we can make that figure 2.

We can see from the explanation at the bottom, what this is trying to sort of document is the impact of ICER ranking on recommendations and its technology appraisal recommendations:

"Decisions are ranked by ICER, with NICE decisions to 'recommend' shown in blue and to 'reject' shown in red. For clarity ..."

I think it is just a sample set is being shown.

So we can see that even below the £20,000-£30,000 range, there are lots more red lines than one would expect, so it does happen sometimes, as you have said,

that they reject it below the threshold.

Could we go to page {XF3/36/12}. I would like to go to the third paragraph under the section that is 3.3:

"Relationship between ICER and probability of NICE recommendation."

If we could blow that up a bit for everybody.

So the third paragraph, I am just going to read it out so I can ask you some questions about it.

Dr Skedgel, actually, I think this paper was referred to in one of your reports. I assume you are very familiar with it. I am sorry, I should have asked that.

A. I would not say very familiar, but I do think I have read the paper in the past.

Q. Sorry, I should have asked that at the start. I just wanted to check before just reading out a paragraph to you:

"The decisions that were poorly predicted by our models were generally rejected because of substantial uncertainty or included statements within the guidance suggesting that the committee believed the ICER to be at/near the top or bottom of the stated range."

So NICE can still reach a negative decision if it does not have confidence in the analysis done if it is concerned about uncertainty?

A. Correct, yes. I think all the speakers yesterday

pointed out the non-deterministic nature of the ICER in this context.

Q. It can also reach a negative decision if the committee thinks the ICER is at or near the top or bottom of the relevant range so it is concerned that it is at the borderline effectively?

A. Yes, yes, I can accept that.

Q. The next point I would like to discuss with you as part of this hopefully not never-ending topic on thresholds is your position on the interpretation of the thresholds and we touched on that in the start of the questions and I just want to be really clear about what opinions you are and are not able, and then given -- able to give, then actually are giving. This is where I am going to need your help in particular.

So starting with the basics again, I understand your position to be that the QALY analysis is a useful guide to understanding the value of phenytoin at its new price?

A. That is my position, yes.

Q. But when you are talking about value, you are talking about value as expressed by NICE's QALY analysis?

A. Yes.

Q. Not in terms of any other concept of value?

A. Correct, strictly in terms of NICE's assessment of

value.

Q. So there are two particular aspects of the evidence that I need to clarify with you, mostly in order so that I am very clear and we are all very clear exactly what we are talking about.

The first is about the extent to which you were giving an opinion on the relationship between willingness-to-pay and the informal or guide thresholds used by NICE.

Can we go first to paragraph 4.1 of your second report which is at {XE3/2/3}. If we could focus in on the paragraph at the very bottom of the page. If I could ask everyone to read that paragraph. (Pause)

So in this paragraph, I will just read out the bit that I am focusing on, you say that NICE's acceptable range of £20,000 to £30,000 per QALY gained:

"... represents a good use of NHS resources and therefore what its users (ie society) would reasonably pay for a unit of health gain, regardless of the age of a technology or its place in its lifecycle."

So this suggests that you are giving an opinion that even if the cost per QALY is above £20,000, society would be reasonably willing to pay the price as long as it is below £30,000?

A. Yes, that is my opinion based on my understanding of

NICE's explanation of its threshold and its methods.

Q. So you are giving an opinion on what QALY means in terms of reasonable willingness-to-pay?

A. Yes.

Q. Could we then go to paragraph 6 -- actually, no, we do not need to do that.

Could we go, I think, more simply just to paragraph 15.2 of your position paper, which is at {XE6/1/4}.

If we could focus in on paragraph 15.2. If I could ask everyone to read it. (Pause)

There what you seem to be saying, Dr Skedgel, is that you:

"... agree with Professor McGuire that NICE does not see itself as applying a legal test of economic value. It also does not ask what the NHS (as the customer) would pay. NICE does, however, ask whether a health technology represents 'a good use of NHS resources' ..."

That is the point we have already discussed. But then you say:

"Whether, by extension, that means that a price is 'reasonable', or one that the NHS would 'reasonably pay' is a question of law. From my perspective as a health economist, however, there is a clear connection between deciding that a drug is a 'good use of ... resources'

and deciding that the price is a reasonable one."

So here you seem to be saying you are not giving an opinion on whether or not it would be the price that it would be reasonably willing to pay or be a reasonable one to pay, so I just want to be very clear what your opinion is and what you feel able to give as an opinion as a health economist.

A. Sorry, could I ask you to re-ask the question?

Q. Of course. Could we have potentially -- I will get the reference for it again -- paragraph 4.1 up on the screen and have the two together, please.

So 4.1 is at {XE3/2/3}. If we can keep 15.2 and have on the other side {XE3/2/3}, and so where my difficulty is, Dr Skedgel, is I want to be very clear exactly how far you are going in the opinion you are giving, and in my reading of the first one, you are prepared to say that if you fall within NICE's range, that therefore means it is an indication of what you as a society would reasonably pay for a unit of health gain, so you are giving an opinion on whether it talks about willingness-to-pay, reasonable willingness-to-pay, but then when we get to 15.2 on the right-hand side, you seem to be saying that that is a question of law and that all you are saying is that there is a clear connection between the two, that the drug is a good use

of NHS resources and deciding that the price is a reasonable one.

So I just want to be very clear what it is that you are saying and what you feel able to say given your instructions on the law.

A. With respect to 15.2, my point is I agree with Professor McGuire that NICE is not assessing the economic value of a treatment in the context that I think the people in this room today are concerned about it, but from a health economist's perspective, I think what NICE views as a reasonable price to pay for a unit of health is informative to the problem that you are dealing with today.

Q. So you are not saying that just because a drug falls within either the threshold range for TAs or under the 20,000, you are not saying that by dint of that, that is a price that the NHS and society would be reasonably willing to pay; you are saying it is relevant to assessing that?

A. I think I am struggling with the reasonably willing to pay. My understanding of how NICE approaches its value assessment is it has laid out £20,000 to £30,000 per QALY as a reasonable use of NHS resources, and from my perspective, as a health economist, I take that to mean it is a reasonable price for a unit of health.

I accept that I think health economists and competition lawyers use "reasonable price" to mean different things, but strictly from my perspective as a health economist, I believe what NICE views as a reasonable use of NHS resources perhaps has bearing on the legal question that you are dealing with.

Q. Thank you, Dr Skedgel. I just wanted to be very clear whether or not you were giving an economic opinion as to this legal question of reasonable willingness-to-pay because there is slightly different language used between the two paragraphs, but I think you are being very clear that that is not what you are doing.

A. I do not think that is what I am trying to do, no.

Q. Can I also just clarify a related point on the substance. I am sorry, I need to show you again two passages of your evidence. If we could first on the left-hand side, can we go to slide 6 of your teach-in. It is at {XE7/8/6}. I am focusing on the second bullet point. There you say that what cost benefit analysis does in healthcare decisions, it:

"Seeks to estimate the value of a health technology to a healthcare system. In this, health economics departs from conventional cost-benefit analysis by largely rejecting willingness-to-pay ... as the only appropriate, or even most appropriate, measure of

value."

QALYs are the preferred measure.

So am I right to understand that this is saying willingness-to-pay is just not a relevant concept in this health economics scenario?

A. Not relevant might be overstating it, but it is not our primary measure of value in the way that it is in other branches of economics and cost-benefit analysis, correct.

Q. I think that helps within this next bit. Can we go to yesterday's transcript, so {Day14LH1/60:14-25}. Could I ask you to just read -- perhaps read from line 10 because that is where you get the question, essentially from the President. (Pause)

I want to understand how these two bits of evidence that we have looked at work together because I understood the point on your slide and from your teach-in that willingness-to-pay is not really a central concept here, but then here in this passage you seem to be saying that the way to understand the QALY analysis is it is about societal willingness-to-pay for health.

Can I just understand what you are meaning by "societal willingness-to-pay for health" here and how it relates to your suggestion that QALY is not really about that. If I could just ask you to explain your position.

I am giving you a clear run, which we do not normally do in cross-examination, but I just want to try and understand your position on where willingness-to-pay fits in.

A. In my slide I am distinguishing the method of willingness-to-pay which could also be called contingent valuation from QALY analysis which we conduct.

So in my slide, I am distinguishing between the methods we use, but there is still, even within the QALY approach, there is still a threshold that economists typically refer to as the willingness-to-pay for a QALY.

So I think I am distinguishing the method and saying health economics tends not to use the method, but there is still a threshold that we call the willingness-to-pay for a QALY.

Q. So I think from everything we have been discussing your position on the thresholds is that it is some form of indication of what society is willing to pay, but it is not a complete answer, is I think what you are saying. Is that a fair way to summarise it?

A. Could be a complete answer to what question?

Q. So in terms of trying to predict -- so say I am trying to predict what the NHS would have been willing to pay for phenytoin in 2012, that is essentially the exercise we are trying to do, subject to competitive conditions,

I think what you are saying is that what the QALY thresholds -- all that they do really is provide an indication of what society is prepared to pay for a health economic unit?

A. Yes, and as you say, I have used the term "rule of thumb". It is a guide, but not a hard rule, correct.

Q. I just want to be very clear, and I do not think you are saying this, but I just want to be very clear that you are not because I will need to cross-examine you on it if you are, is I do not think you are saying that so long as the drug falls under either £20,000 or £30,000, the maximum of the range for technologies and this sort of key £20,000, then that price should, by dint of that, be deemed reasonable for the NHS to pay. I do not think that is the opinion that you are giving; is that right?

A. I think my position may be slightly more nuanced, that it is, in the first instance, an indication that it is perhaps a reasonable price, but it is not in itself, I would agree with you, the end of the story.

Q. I think, Dr Skedgel, that is what I was trying to get at with complete earlier but I think we are on the same page in understanding each other.

Just on paragraph 4.1 of your second report which we have looked at, it might be useful for us to bring it back up again, if I just grab the reference, {XE3/2/3}.

You say there:

"... £20,000 to £30,000 per ... (QALY) gained represents a good use of NHS resources and therefore what its users (ie society) would reasonably pay..."

Now, I just want to clarify, I think we agreed earlier in the £20,000 to £30,000 range, NICE makes clear that it will consider a range of other factors before it decides whether or not to recommend the technology?

A. Correct.

Q. Is the fact that it is just within the threshold range sufficient to be an indicator of what the NHS would be reasonably willing to pay, or should that really be referring to below the £20,000 threshold where it is normally allowed at that rate?

A. Yes, I think it is fair to say the basis of the decision changes as you move further away from being below £20,000 to towards £30,000.

Q. I also just want to check before we move on to a slightly different part of the thresholds topic. Can I also check whether you agree with me that QALY analysis does not assess what society or what the NHS would be reasonably willing to pay in a competitive market?

A. No, we take no account of competition or competitiveness

in a QALY analysis, no.

Q. Now, finally, I promise, on the thresholds issue, Dr Skedgel, I want to see what we can agree about how the QALY thresholds we have discussed are used by NICE and how they should be interpreted in terms of willingness-to-pay. So we have discussed that they are not hard edged as a rule of thumb, so we do not need to talk about that again.

From yesterday, I think everyone agrees that the informal thresholds which are used are based on limited empirical evidence and they have an uncertain history.

A. I would accept that, yes.

Q. That is the dirty secret from yesterday. The roughly £20,000 figure has not been changed in over two decades?

A. That is correct.

Q. I think you said yesterday that it is hard to see there is a clear justification or clear reason why it is £20,000 and not £25,000 or not £15,000?

A. That is also correct.

Q. So can we take from this that QALY analysis is really just relevant as a comparator tool for NICE's assessment, that that is essentially how far they go in how useful they are for NICE and for society?

A. Sorry, can you (inaudible) the question?

Q. I am sorry. I think essentially what I am just asking

is essentially, because it is not a hard -- there is no fixed threshold, it is essentially just a comparative tool to assist NICE in deciding whether a drug should come on to the NHS or where it fits in the guidelines?

A. I think I would take the position it is a bit stronger than a decision aid. I think from the figure you put up there is a clear correlation, if nothing else, between the ICER and the probability of an approval, but I do agree with you again that it is not a strictly deterministic mechanism.

Q. I just want to show you a paper that I actually believe that you cite in paragraph 16 of your second report, but I just would like to go to the actual document itself just to see if you agree with some of the points made in this report.

Can we go to {XF3/27/1}, please. This paper is from 2009. I wanted to note that on the first page. Could we note at the top that this is a paper by Michael Rawlins et al. Professor Sir Michael Rawlins was the founding chairman of NICE. I think he was chair from 1999 to 2013. That is who this is?

A. Yes, I am aware of Michael Rawlins.

Q. Yes. The passage you refer to in your second report is actually at the bottom of page {XF3/27/2}, so if we could look at that first. I think it is the final

paragraph on page 2, and I think all that is really doing is summarising NICE's case-by-case approach to the thresholds, but I would like to focus on the previous paragraph which is I believe what you are referring to in your second report when you say that "NICE is careful to avoid suggesting there is an absolute threshold."

If I could ask everyone to read that first paragraph under "The case-by-case approach", and the points 1 to 4. (Pause).

So, Dr Skedgel, I just want to take each of the points in 1 to 4 in turn.

The first one is:

"To set a threshold would imply that efficiency has an absolute priority over other objectives (such as fairness)."

I think we discussed that and we agree that NICE takes wider factors into account?

A. I agree.

Q. So you agree with that reason for not having a hard threshold?

A. Yes, I mentioned the equity objectives.

Q. Yes. We have discussed, again, the weak empirical basis, I think we have already agreed that that is a reason why there is not an absolute threshold.

A. Correct.

Q. Then just the third and fourth. I am just going to read them out and then ask you some questions about them:

"Many health technology suppliers are monopolists and a threshold could be taken to imply a definite price that could discourage price competition."

And then:

"Rigid adherence to cost-effectiveness threshold would create the impression that NICE's advisory bodies accept all the calculations that have gone into estimating a technology's cost-effectiveness. It would therefore remove their discretion to assess costs and benefits appropriately when modelling has reached its limits."

I just want to ask you a very open question: do you disagree with either of the points made in those two points, 3 and 4?

A. I do not. I do not disagree.

Q. A key concern of NICE is therefore to avoid the impression that the threshold amounts to a definite price that could be charged by a monopolist?

A. Again, sorry, do you mind asking --

Q. A key concern of NICE is to avoid the impression that the threshold amounts to a definite price that could be charged by a monopolist. That is the point in 3, is it not?

A. Yes, I think that is a fair statement, yes.
Q. The concern being that if you are a monopolist holder of the rights to a drug, there is no price competition, so you would create a situation where, with facing no price competition, a monopolist would be free to charge whatever they want as long as it passed the £20,000 threshold?
A. Yes, and I think I have made that point in a couple of my reports, that despite NICE's reluctance to provide that reference point, I think in practice I have shown that it is quite often used as a reference point for headroom analysis and economically justifiable prices.
Q. We will certainly come on to headroom analysis momentarily as I am sure you predict, but in terms of what NICE is trying to do, it is deliberately not saying to manufacturers: all you have to do is pass the threshold and you are fine; that is not what the Department of Health is saying to manufacturers through NICE.
A. Yes, I think that is an appropriate interpretation of that point, yes.
Q. So NICE does not want to give monopolists a ceiling price that they can just get away with?
A. Actually, I think the language you used in your question is a useful one. I think to some extent they perhaps do

want to give a ceiling price. Obviously they do not -- they would prefer that not everyone prices at that ceiling, but it is certainly an indication that we are not willing to consider beyond this ceiling.

Q. So in a sense you think about it as the thresholds tell you what you really cannot go above, but it is not making you any promises below?

A. Yes, I think that is a fair summary.

Q. The same would apply -- we tend to focus on technology appraisal because that is in effect what you have done for phenytoin, but the same concerns would, of course, apply to the £20,000 threshold in guidelines: they would not want to be signalling anything goes as long as you hit the target or just under it?

A. Yes, I do not think that would be their desire or preference, correct.

Q. Can we now go to {XF3/24/1}. This is a paper by McCabe et al about the NICE cost effectiveness threshold, it is a paper from 2008. You do refer to this literature in paragraph 21 of your second report, but I just want to check how familiar you are with it to make sure I give you enough to read before I ask you any questions on a bit of it.

A. It is been a while since I have read this in detail, so I would appreciate a bit of context.

Q. No problem. So can we go to page {XF3/24/2}, then, at the bottom on the left. There is a heading, and I think then from your indication the first thing to do is just to ask you to read the section from where it says:

"What the Current Methods Guide Says."

Sorry, I cannot now see the top of the other column. If you could just read down to, I think, the paragraph just under the quote -- so section 2 starts, there is a little first paragraph, if you could read the quote and the following paragraph after that.

A. So read to "legitimate reference for the Committee"?

Q. On the right-hand side it starts with:

"The guide then goes on to consider a range of possible other factors ..."

I do not think we need to read that bit because we have already gone over those bits. So it is from:

"2. What the Current Methods Guide Says."

The first paragraph starts with:

"The 2004 Methods Guide ..."

There is then a long quote and the paragraph immediately after that.

A. Okay. (Pause)

Okay.

Q. I just want to focus on what is said in the quote first. I think the first thing is it is right, I believe, that

there is considerable debate over what the threshold should be. We have already touched on that.

A. That is absolutely correct, yes.

Q. In fact, Professor McGuire explained in his teach-in yesterday that other bodies such as the Department of Health use a lower threshold of £15,000; are you aware of that?

A. I was not specifically aware of that, no.

Q. So what is being said in this quote, I think, from the 2004 guidance, is that NICE does not have all the necessary information about the health programmes to allow it to set a fixed threshold, so you would need a lot more information about the health programmes if you were going to attempt to set a hard threshold?

A. Correct, and in particular, you would need information on the cost effectiveness of older medicines and generics, yes.

Q. And also if NICE were to try to set a threshold in this way it would need to change it over time to take account of how the NHS budget changes?

A. Correct, yes.

Q. And presumably for inflation as well?

A. Well, you raise the point that the threshold has not changed since it was first defined, and that has been a point of contention again among health economists who

do occasionally question why the threshold has not risen with inflation.

Q. So really this goes to, and I think a point we are agreeing, but I just wanted to make sure that you had seen this, that what NICE is saying is: look, we use the comparators as a reference point, but it is in no way determinative of our decision-making because it is not a perfect tool?

A. Correct, I accept that.

THE PRESIDENT: Dr Skedgel, I just want to ask you this: if you were being asked to devise a rational way of causing the threshold to vary over time, how would you do it?

A. So I can give you the theory of the threshold. The threshold -- there are two critical pieces: there is the budget and there is the threshold, and the theory of cost-benefit analysis says rank all the programmes you are interested in from the most efficient to the least efficient, in this case the cost per QALY or the inverse, the QALY gain per pound spent, they are equivalent in terms of efficiency. You rank them from most to least. The point at which you run out of budget is the threshold. The two -- in theory, the two cannot be separated: the budget determines the threshold or conversely the threshold determines the budget. If you say I want to fund everything that meets a particular

threshold, you lose control of your budget. If you set a specific budget, you lose control of your threshold.

NICE is walking a tightrope of trying to impose both of them at the same time.

THE PRESIDENT: Yes, so what you are saying is if you have a threshold which is very, very low in the sense that only extraordinarily good value drugs make it through there, you will stretch your budget far further but in fact you will end up with fewer drugs being paid for because the threshold is so stringent?

A. Precisely.

THE PRESIDENT: On the other hand, if you adjust the threshold differently so that it is easier to pass, you will end up spending more money, you would either have to increase your budget to afford the same number of drugs, or you will have to --

A. I might pause at where you said the same number of drugs.

THE PRESIDENT: Yes.

A. In principle, you should be able to buy -- if you increase your threshold, you will allow more drugs into the system.

THE PRESIDENT: Yes.

A. But not necessarily pay more for the same number of drugs.

THE PRESIDENT: Sorry, let me see what I said just to make sure we are on the same page.

Yes, well, I suppose what I am saying is that you will have more drugs that qualify, you will have ranked them according to the factors we have been discussing --

A. Yes.

THE PRESIDENT: -- and you will erode the budget by reference to the first in line, the second in line and so on, and at some point you will run out of money, and if the threshold is more generous in the first situation, you will run out of money quicker --

A. Yes.

THE PRESIDENT: -- and you will have to work out: do I increase the budget in order to get the same number of drugs as I got under the previous situation, and of course, you will get more because you are allowing more in.

A. Yes, that is the straightforward intuitive interpretation.

THE PRESIDENT: I understand. So going back to my original question about how you would adjust the threshold to the budget, I think your answer to me is that in the nicest possible way, my question was utterly pointless because the threshold is not adjusting to anything related to inflation or value or anything like that. What it is

doing is it is constituting the increment by which each drug that passes that threshold erodes the budget.

A. You could approach that problem from either side.

THE PRESIDENT: Indeed, I quite appreciate that you have two variables, and the combination of the two affects how many drugs are fed into the system.

A. Yes.

THE PRESIDENT: I am focusing not on the budget but on the threshold element, so if you assume, which I accept is not the case, but you assume a rigidly fixed budget, the effect of varying the threshold means that you have a different drug constitution in terms of what is purchased than in a different situation.

A. Yes. We call it the bookshelf analogy. So you could imagine a very tall book at the extreme left-hand side, this is the very efficient programme, and then efficiency goes down. So as you increase the threshold, make it more generous, the number of books you can have on your bookshelf goes down.

THE PRESIDENT: Yes, I am grateful, but it does mean that the sort of questions that one would ordinarily apply to thresholds, namely inflation, for example, is not really a meaningful point for adjusting the threshold?

A. Again, that is a point of ongoing debate within health economics of how inflation should or should not feed

into the -- my understanding, I am not an expert on the threshold, but my understanding of the justification for why it stayed is that as a ratio, if we are assuming all prices -- prices and budgets are increasing at the same rate, that we can treat this almost as a real number rather than a nominal number, there is debate about that.

THE PRESIDENT: But we do learn from the fact that the threshold has remained unchanged something about NICE's understanding of the threshold?

A. One view would be that it has become more stringent over time because costs have gone up, but the threshold has not. Another view would say: well, it is all balancing out because the budget is increasing at the same rate as inflation, but that is not necessarily the same as the same rate as the cost of production.

THE PRESIDENT: Well, it would depend. I mean, if each particular drug increased in exact proportion to budget, then it would not matter, but in any other case, it would make a difference.

A. It would seem to make a difference, and there is, as you would imagine, endless debate over what that difference is.

THE PRESIDENT: I am grateful. So my question was not completely pointless, I am very grateful.

PROFESSOR WATERSON: Could I just come in here? You talked a little bit back about a clear correlation between the likelihood of a product being accepted and the QALY analysis, and also the previous paper that we had up had a similar language about this. So am I to understand this in a sort of statistical sense that there are a range of things being considered by NICE in these analyses and, if you like, if one comes in at £2,000 per QALY, it gets a big tick, but if it comes in at £15,000 it will get a potential tick but there will be more investigation and so on, and so there will be, within the set of products that are approved, new, I guess, there will be new things all the time, there will be quite a range of QALYs, potentially?

A. Potentially, yes, and, as you say, as you get closer to that £29,000 and £30,000 per QALY, you had better be delivering something beyond simply QALY gains to ask for that cost per QALY, yes.

PROFESSOR WATERSON: Thank you, that is very useful.

MS MORRISON: This is essentially me stealing a question from Professor Waterson from the economists' hot-tub so I should acknowledge that, but he was using a threshold of £12,000, but I will keep to £20,000 first for simplicity, because that is really what we are talking about here, but if every single drug on the NHS -- this

feels like a silly question, but if all the drugs priced on the NHS were priced up to the £20,000 threshold in real life, that would blow the NHS budget, would it not?

A. I mean, certainly from the question the President asked, that is correct, there would be fewer books on the shelf, fewer drugs in the system, within the existing budget, yes.

Q. So essentially what happens is NICE does its role, but presumably the Department of Health and others are relying on other policy levers to control the prices that are feeding into that process in other ways to make sure at least some of them are below £20,000?

A. That is my understanding, again, I am not an expert on the other mechanisms that the Department of Health has at its disposal.

Q. I did acknowledge that and I am not going to ask you anything on that.

I just want to give you a chance to comment on this in all fairness. I just wanted to show you slide 8 from Professor McGuire's teach-in from yesterday which is at {XE7/7/8}.

I want to just focus on the example he gives. There is various main bullet points, and it is the one:

"Generics will already be on the market."

Then his example is the second bullet point

underneath that, he is making the point:

"If this were done the NHS would soon be bankrupt ..."

So it is the question I just asked, and he gives the example of metformin. I just wanted to give you an opportunity to comment on that analysis with anything that you wanted to say about it being incorrect, or do you accept that that is at best a rough assessment of what the kinds of implications it could be for drugs already on the NHS?

A. I accept Professor McGuire's mathematics on this, but I question the plausibility of the scenario he lays out. I did see this in his teach-in yesterday, and I had a look online last night. By my count, there is 22 generic manufacturers of metformin listed on the BNF at the moment, so I find it implausible that --

Q. I think Professor McGuire would agree it is an improbable scenario that anyone is going to try to price back up to that threshold with 22 generics in the market. I just wanted to give you an opportunity to comment on the maths, because it is just an example of the point.

THE PRESIDENT: Well, no, I think we are asking for more than that, are we not, because your point, Dr Skedgel, is this: that the maths may very well be right, but you

will never get to that level because of competition between generic producers of drugs which will mean that the price will not trend up to the maximum, it will be at some level that is competitive?

A. That is correct, sir, and even beyond that, how NICE deploys metformin would change. Right now they have an implicit or an explicit understanding of the value of metformin to particular patients and because the price is so low, there is a relatively low threshold to put someone on metformin. If the price of metformin changed dramatically, I think as Mr Hawkins pointed out, a dramatic price rise like this would perhaps trigger a guideline review that would change how metformin was deployed within the NHS, which I think in itself would mitigate the budget impact of this price increase.

THE PRESIDENT: Not just that, but it would in and of itself operate as a change in the demand curve which would have an effect on price.

A. Yes.

THE PRESIDENT: Because effectively if you are selling at the low price, 500,000 units of whatever product it is but the price triples and the guidelines then change and you sell 50,000, well, your price may well have been -- your price increase may well have been an uneconomic one in the sense that your total revenue will be less?

A. Yes. Going back to my undergraduate microeconomics and price elasticity, price demand elasticity, yes, that seems like a fairly natural expectation in a reasonably competitive market, yes.

THE PRESIDENT: It is just that the demand curve in this example is not informed by the individual choices of purchasers of a product. It is informed by the assessment of NICE as to what is and what is not good value for doctors to prescribe given the change in circumstances in terms of value for money and all the things that NICE does?

A. Yes, so again, I am by no means a medic and have very limited understanding of metformin, but my expectation would be NICE would identify a particular -- a sub-group of everyone who is receiving it now that would benefit more from metformin and try and segment that bit of the patient population that said: this, now, is the only people who will be eligible for metformin and we will change those eligibility criteria or guideline recommendations.

THE PRESIDENT: Thank you very much.

MS MORRISON: My question on this is essentially: this is an example, then, of the fact that NICE is not saying to every generic supplier it is okay to price up to £20,000, there is an expectation that competition will

do its work separately?

A. I am not sure I am prepared to accept that this is NICE telling generic manufacturers that it is not -- again, going back to our earlier discussion, I think it is saying we do not accept anything beyond this, and obviously we would prefer that it is well below this.

Q. Can we now go back to page 7 of the McCabe article that we were looking at earlier which is at {XF3/24/7}.

Now, given what you said earlier, can I ask you just to read the whole of -- there is a heading:

"4. Implications of Setting the Threshold to Optimally Exhaust a Fixed Budget."

Could I ask you to read the rest of this page and then when we get to the next page a little bit over the page? (Pause)

It is just a little bit over the page where it says:

"... by, for example, facilitating perfect price discrimination."

Do you agree with me that this is focusing on what happens if patent holders price to the QALY threshold; that seems to be the concern that is driving this discussion?

A. Yes.

Q. Given what you said earlier about you have not -- in terms of the scope of the discussion, I just want to ask

you one simple question: as a health economist, can you just confirm whether you agree with the analysis here that if a manufacturer prices to the threshold they are capturing the full value of the innovation?

A. I have seen this argued before in different contexts, and I accept the analysis if £20,000 is taken as the maximum willingness-to-pay. Where I perhaps deviate from this argument is NICE makes it clear that in some contexts it is willing to pay up to £100,000 and I think Professor McGuire made the point that in extreme cases that can go as high as I think £300,000. So I think saying £20,000 represents the absolute ceiling willingness-to-pay is not correct and therefore there is still the potential for consumer surplus beyond £20,000.

Q. I fully appreciate that there are other thresholds and they are higher, but let us take first if this is a £20,000 threshold for guidelines. If someone prices to that threshold under the guidelines process, then they are capturing the full value of any innovation, that threshold is £20,000?

A. I am not sure I accept necessarily that £20,000 represents the full value of the product. They may have priced to £20,000, but I do not think in itself that defines the full value of the product as £20,000.

Q. So we need to consider other factors, then, to come to

a view of how the value has been --

A. I think so.

THE PRESIDENT: How are you defining "value"? I mean, you are defining "value" as the equivalent of the threshold?

MS MORRISON: Sir, actually, I was defining value here in terms of the threshold per QALY, but thinking about value as the QALY, so that is what I am trying to get at and the willingness-to-pay that we have discussed is to a degree inferred by that -- I appreciate that Dr Skedgel's evidence is clear that he is not saying it equals willingness-to-pay, so that is what I was trying to give him an opportunity just to comment on what he thinks of this analysis about producer surplus.

THE PRESIDENT: Your question was if someone prices to that threshold under the guidelines process then they are capturing the full value of any innovation. Now, that is, I think, equating the value to the price; that is the premise of the question.

MS MORRISON: Sorry, there I am equating a value to the cost efficiency, sorry, sir, just to be very clear, because I think what is being discussed here is there is essentially if you are below the threshold, there is an efficiency gain because you have, in a sense, a drug that is more cost effective, so there is a question about how that is shared. If you price up to the

threshold -- I am looking at Dr Skedgel -- if you price up to the threshold, what this article is discussing is that then the manufacturer is reaping the benefits of that efficiency gain, whereas if it is below, there is some degree of sharing of consumer surplus.

THE PRESIDENT: All right, so you are talking efficiency gain, not value?

MS MORRISON: Sorry, yes, sorry, sir.

So, Dr Skedgel, I just want to ask you that again, then, in terms of referring to it as the efficiency gain: who is capturing the efficiency gain if they are pricing up to the threshold?

A. Yes, I can accept framing it as efficiency gain that that gain is going to the manufacturer.

Q. I apologise, Dr Skedgel, I appreciate that was confusing, I am sorry. The word "value" has far too many meanings in these appeal proceedings.

I was about to move on to a different but related issue, so I think that might be a good place to stop, sir. I realise that I have gone past when we should normally have broken.

THE PRESIDENT: Thank you very much. We will rise for ten minutes. Thank you.

(11.38 am)

(A short break)

(11.57 am)

MS MORRISON: I am going to move on from thresholds, I am sure you are relieved to hear. I would like to move on discussing the meaning of the thresholds and discuss a fifth topic: QALY analysis and pricing.

I want to discuss first your evidence that NICE has an indirect influence on pricing when it comes to technology appraisals. I would like to turn first, if I can, to paragraph 14 of your second report which is at {XE3/2/7}. I think the last five lines is what I wanted just to ask everyone to read, because I think that is essentially where you explain what the process is. If I could ask everyone to read that.

A. Sorry, where am I starting?

Q. Sorry, the last five lines starting:

"Essentially, headroom analysis is the analytic process of ..."

It is just to the end of the paragraph. It is just to set the stage of where we are and what we are talking about as headroom analysis. (Pause)

Dr Skedgel, would it be fair to say that when you are referring to value-based pricing or headroom analysis, that is a form of pricing that applies in the lead-up to market entry for a drug?

A. I would say it applies at the time that they submit to

NICE, they submit their TA to NICE.

Q. So it is about submitting your TA to NICE to be able to -- I think you talk in one of the parts of your report about it being about access to the UK market, it is an obstacle that you have to get past?

A. NICE approval, yes.

Q. If we are talking about an unbranded generic like phenytoin, it seems unlikely, because it is not going -- it has not, at least, been submitted for a technology appraisal, that anyone would be engaging in value-based pricing, because it is about that point of getting on to the market?

A. I do not think I would agree with that in its entirety. Obviously there has been a price change. I am -- as I say, I am not privy to any information that they did conduct any sort of headroom analysis, but equally I cannot rule out the possibility that they would have in setting their new price.

Q. We have no evidence of any of that in this case. I wonder then if we could have a quick look at that -- I have no idea how to say this name, it is Boudewijns et al. It is a literature that you rely on in your report, so I wondered if you knew better than me how to say it, but let us go to it first, {XF3/63/1}. I am not trying to catch you out on the name of anything.

This is it. Can we go to page {XF3/63/2} of this paper, please. That should be it. Can I ask everyone to read the introduction down over the page to -- there are little notes in brackets and there is note 11, if we could read to note 11. If we could perhaps put the next page on the side beside it, it would make it easier for everyone. (Pause)

This is talking about headroom analysis as something that happens during the early stages during the development of health technologies. It is not suggesting that it happens once the drug is already on the market.

A. On the market, no, but I think as I read it -- sorry, there was a line where it says it most often happens early in the stage, something to that effect.

Q. We will move forward. Could we move to page {XF3/63/8}. Under the heading "4.4 Recommendations", and the first paragraph, what it says is:

"The headroom analysis is developed to rule-out health technologies that are unlikely to be viable in the future. It can be used by companies to avoid wasteful spending or to convince potential investors of the room for improvement in current practice, for funders to preclude health technologies that do not have the potential to be cost effective, or for researchers

to assess whether there is a proof-of-problem and to justify public spending. The deployment of the headroom analysis will depend on its aims, the stage of development, and resources available."

But again, this seems to be really just about these analyses being done before the drug enters the market, so it is not about something that a supplier, like Pfizer or Flynn, would do, when they are trying to reprice a drug that is already on the market.

A. I agree with you that this paper is discussing headroom analysis in the context of early feasibility-type studies. As I have also said, I cannot comment on whether Pfizer or NICE did conduct such an analysis, but I can also confirm that in my previous -- in my modelling role at my previous consultancy, we regularly conducted these sorts of analyses to inform pricing as part of a NICE submission.

Q. So it is part of a NICE submission, so it is part of the technology appraisal process, that is where you have experienced it having a --

A. Prior to submitting, but setting the price that would go in as part of the submission.

Q. So it is that prior process before you submit?

A. Yes, in preparation for the submission, yes.

Q. You made one new point yesterday on NICE's role in the

price-setting in the context of guidelines, so I just wanted to have a quick discussion about that before we move on.

Could we go to slide 25 of your teach-in which is at {XE7/8/25}. Can I ask everyone else, I am sure you are familiar with it, Dr Skedgel, to remind themselves of the last bullet point.

I think you are saying here, and you said yesterday, that NICE also has an indirect influence on pricing through this kind of a comment.

Could we -- before I ask you some more questions about that, I want to show you some documents. Could we now turn to {XG/121/214}, please. It is the third full paragraph on the page, it starts:

"Other AEDs ..."

If I could just ask you to read there. Sorry, I should have said, this is from the 2012 guidelines which you were quoting from.

A. Okay.

Q. I apologise, I should have said that. (Pause)

So the anticipation was that it was going off-patent, the genericisation of the product would lead to some level of drop in price in levetiracetam. I made Professor Sander laugh a lot practising for this hearing. So I will ask that again.

So the anticipation was that genericisation would lead to some level of drop in levetiracetam, but it was not known by how much, and that was the issue that NICE was troubled with in 2012.

A. Okay.

Q. So what the committee was doing was anticipating the benefits of competition; it was not itself giving an indication designed or intended to provide a guide on price.

A. Offering my opinion here, I think I would, as a manufacturer, I would interpret that as a fairly strong signal of what they would expect an acceptable price to be.

Q. What they are saying is that it needs to go below a certain level, but the price is going to be determined by generic competition, so NICE is not trying to influence any particular manufacturer of what price they should end up at; that would be determined by competition, would it not?

A. So I recognise collusion is a big issue in pharmaceutical pricing, but at the same time, economics has a branch known as game theory where you try to predict what your competitors will do and respond in response to what you believe your competitors will do.

So I do not think I accept that competitors, even,

you know, genuine legal competition I think would interpret that as a signal of where their price should be, would need to be, to gain substantial market access in the UK.

Q. Could we then go to figure 6.14 of the Decision which is at {XA1/3/370}.

THE EPE OPERATOR: This document only has 355 pages.

MS MORRISON: It might be that it is {XA1/1/370}. Let us try that. I am sorry for that. That was what I was looking for.

Figure 6.14. So this is the total number of levetiracetam (generic) and Keppra (brand) tablets that were dispensed across from 2004 to 2021, and we can see that the red bars, and this is from the key at the bottom, the red bars are the Keppra-branded product tablets, that blue is the levetiracetam generic tablets, the body of them.

You can see the blue starts in 2011 but really takes off in 2012, so that is what was anticipated by NICE.

Could we then have a look at figure 6.16 which is a couple of pages on at {XA1/1/373}. The orange line is levetiracetam, and you can see where the price was at 2011, so this is the prices for generics, and you can see what happens with -- you can see how the price essentially plummets, the orange line.

Does that not suggest, given the degree to which the price plummets, that the indication NICE gave about having below 50% had no influence on this pricing, generic competition pushed the prices down substantially?

A. Yes, I would accept that this appears to be much greater than a merely a 50% decline, yes.

Q. So you would agree, Dr Skedgel, that the likely cause of that price reduction was the generic competition (inaudible) to do with what NICE said?

A. Yes, it does not appear that that particular NICE note had a lot of influence on the final price.

Q. Are you aware of any other examples in the guidelines of NICE giving an indication like that one?

A. Not offhand, no.

Q. Now, my sixth topic that we are going to move on to is essentially about clarifying exactly what your analysis does. I am going to start again with the basics. You have not conducted your own QALY analysis in respect of all of the anti-seizure medications which were available in the 2012 to 2016 period?

A. Correct, we focused on the -- I think in that -- in the 2012 version I think they were called the tertiary adjuvant line.

Q. There is lots of different terminologies, there is

third-line or there is second-line adjunct, but I think we are on the same page, it was the third group of drugs.

A. Yes.

Q. You then added perampanel because that was added as a third-line drug in December 2012, so during the period that we are looking at.

You conclude that phenytoin, even at the higher prices charged in the relevant period fell just below the £20,000 QALY threshold, so I just want to be very clear: you do not suggest that NICE incorrectly classified phenytoin as a third-line drug, you do not dispute that characterisation?

A. Not at all, or I take no position on that.

Q. Can we go first to paragraph 97 of your first report which is at {XE3/1/25}.

Now, I acknowledge at this stage you had not conducted a sensitivity analysis that you do in your second report, but can I just ask everyone to read paragraph 97. (Pause)

I just wanted to confirm that it remains your position that small changes in cost or outcomes could change the relative ranking of the comparators, that is what is said in the middle of that paragraph?

A. Yes, I guess to be clear, small changes in the expected

value of those, yes.

Q. Which means I think you would accept that even a small change in your approach, for example, a change to the proportionality assumption, could result in changes to the ranking of the ICERs, is that what you mean?

A. I think the challenge is in defining a small change, so, again, I cannot recall if the threshold analysis was part of my initial report or the second report but, as I showed in the teach-in slides, to me there is enough buffer in what that efficacy estimate would need to be without changing the -- without moving it outside the range of what NICE would consider.

Q. We will come back to the (inaudible) analysis then. Can we now go to paragraph 41 of your first report at {XE3/1/10}. If I could ask everyone to read that paragraph. Again, I am sorry for all the reading.

(Pause)

I want to break it into two steps. In a sense what you were trying to do first of all is put yourself in NICE's shoes as sort of end of 2012/beginning of 2013, that is what you were trying to do in this exercise?

A. In this exercise, I was trying to produce an analysis of the sort that NICE would expect as part of a TA assessment, not trying to put myself in the shoes of NICE as the decision maker.

Q. I see, sorry, that is what I meant, in terms of trying to do that, the QALY analysis as if they were doing it?
A. Yes.
Q. Then you said there in this paragraph you have referred to it almost as if it does not matter whether it is being done as a technology appraisal or as a clinical guideline development. In your position paper you have talked about putting your analysis forward as a hypothetical technology appraisal essentially. Does it matter to you which one it is considered as?
A. No, in my view the analysis -- the -- for me, the material difference between a TA and the guideline is how the economic -- the underlying economic analysis is interpreted and implemented, not in how the analysis itself is conducted.
Q. As we have discussed, though, the implications would be very different in the real world: if it was a technology appraisal it could lead to a statutory requirement to buy, etc?
A. Yes.
Q. But you are focusing on the prior stage of that essentially?
A. Correct.
Q. Now, as we discussed, you are looking at this as if quasi -- I am putting myself in 2013. I just wanted to

check that you are aware that when NICE considered phenytoin in 2012 it did not conduct an economic evaluation of it?

A. I am aware of that, yes.

Q. That was because of the narrow NTI.

A. I understand that, yes.

Q. So just ask yourself: if NICE had decided to reconsider its approach back in 2013, there is at least a chance it would have done the same thing again and just said we cannot do this because of the narrow therapeutic index, is that right? You know -- just when you are thinking about it, that was a possibility, was it not?

A. I can accept it was a hypothetical responsibility, but the subsequent decision -- if we are talking about subsequent decisions, the fact that it was included in the 2022 guidelines I think makes that a very hypothetical statement.

Q. So in 2022 it did consider it, but the result was that it found it to not be cost effective as part of its QALY analysis and that was at a lower cost than the one which you used because it was post the 2012-2016 period?

A. Correct, at a lower cost and a lower efficacy, yes.

Q. That brings me neatly to my next topic. I would like to discuss now the ways in which your analysis departs from the approach that NICE has taken and NICE's conclusions.

You have explained in your reports that due to constraints in the availability of evidence and the time you had to adopt a different approach -- and the time that you had, you have had to adopt a different approach to that recommended by NICE in some respects. That is right, is it not?

A. Yes.

Q. So, for example, you have not conducted a systematic literature review; instead you have described what you have done as a pragmatic review?

A. That is correct.

Q. But that meant, of course, that you missed out Cramer which NICE relied on. That is right, is it not?

A. We did miss Cramer in the first instance, yes.

Q. Now, I appreciate you disagree with Mr Hawkins -- you and Mr Hawkins have a disagreement about the correctness of that decision. Pausing there, before I ask my questions about it, I just wanted to give you an opportunity to respond to Mr Hawkins' comments this morning about the comparison between Cramer and Bill et al, because obviously that has not been flushed out in the paper before the Tribunal.

A. Sure. In fact I think just lower down the screen, the page that is on the screen right now, I make the point that we exclude Cramer not on any assessment of the

quality, but as being non-informative to the model that we were constructing. So we constructed, as Mr Hawkins noted, a two-state model: full seizure-freedom or nothing, a very dichotomous outcome. Given that we were focusing on complete seizure-freedom as the outcome of interest in the model and Cramer does not distinguish partial from complete response, we could find no way to include that in our analysis.

Q. So ultimately, because you adopt a different model, you looked at different studies essentially is I think what you are saying?

A. I think that is fair, yes.

Q. So given that NICE looked at Cramer in 2012 and in 2022, if you submitted your dossier or your instructing client submitted its dossier and you had built the two-stage model which we will come back to and you had excluded Cramer there is a decent chance, is there not, that NICE would say, no, we want to include studies like Cramer and have a three-state model given that is what it has done itself?

A. Again, it is hypothetically possible they could have said that. My interest in building the model was seeking to minimise bias. The issue in Cramer is, leaving aside that we cannot separate complete and full response, they do not report them separately, they do

report a 28% response rate which is higher than the number that comes out of my proportionality assumption of 6.8%.

So I accept that my data sources are not immediately overlapping with NICE's, but I do not accept that that introduced a bias into my result, and, if anything, was probably a more conservative approach to estimating efficacy.

Q. Dr Skedgel, I can reassure you, I am not really talking about degree of bias in the model at the moment. I am just trying to understand the extent to which you accept that by -- we can do them together -- by adopting a two-stage model and a three-stage model and therefore having a different set of studies, if that was submitted to NICE do you accept it would be open for NICE to say we do not like that, we would like a three-stage model, please, with Cramer back in?

A. Yes, and you see more or less the same thing in the other direction: NICE recommended in the cenobamate assessment to move from a five-state to a three-state, so, yes, I completely accept that they could have gone in the other direction with a different recommendation, yes.

Q. I would now like to discuss your proportionality assumption. I understand that you are relying on the

estimate NMA, you proceed on the basis that I think 6.85% is the precise figure that you have included, a patient starting on phenytoin as an adjunct would achieve a complete response to seizure-freedom.

I just wanted to ask, Dr Skedgel: have you had access to the transcript of the live evidence given by the clinical experts, in particular, Professor Walker?

A. I was in the room for the -- for his testimony.

Q. I think I will show you it anyway because I know that my memory would not pick out the precise passage that I am going to refer to. So if I could turn to {Day6LH1/92:} to {Day6LH1/93:} and if we could bring them up side by side, please.

If I could ask you to start reading from the question at 24 on the left-hand side and read through to 11 on the next page. (Pause)

Professor Walker and Professor Sander were agreed that it was about 5% was the figure, and you obviously, at 6.85, are a third to a quarter above that. So if you change your proportionality assumption to 5%, say that Professor Walker was the doctors on the NICE committee and they put it back to you, that could be enough to push your ICER over the £20,000 per additional QALY, could it not?

A. Yes.

Q. Okay, can we go to paragraph 55 of your first report which is at {XE3/1/12}. If I could just ask you to read paragraph 55 in full. (Pause)

Could you go down because it is paragraph 55 we are focusing on which is at the very bottom of the page and I think it goes over the page now, but I cannot really see. If you could put them side by side, sorry.

So what I understand from this passage is that you accept that you have made assumptions that are not in line with NICE's recommended best practice.

A. That is correct.

Q. I just wanted to focus on the bit where you say:

"I note that the only way to avoid these assumptions would be to conduct a full clinical trial of phenytoin in the adjunct setting."

We have discussed that NICE itself did not adopt these kind of assumptions in 2022, so I just wanted to confirm there are other ways of dealing with the evidence gap, for example, in the way in which NICE did in 2022?

A. I am sorry, there is different ways than how NICE approached it or different ways than how I --

Q. I will read out the bit that I am focusing on:

"In developing my assessment of value to the NHS of third-line use of phenytoin for new patients, I have

followed NICE health technology assessment methods where practical. However, I have made a number of assumptions that derive from data constraints and are not in line with NICE's recommended best practice in health technology assessment ..."

You refer to a NICE document there.

"I note that the only way to avoid these assumptions would be to conduct a full clinical trial of phenytoin in the adjunct setting."

What I am putting to you is essentially that there is not only one way to do this; NICE had a different way of dealing with the evidence gap --

A. Oh, yes.

Q. -- and there are other options and NICE's route was one of the available options?

A. NICE's assumption -- well, in the absence of the clinical trial, you had to make an assumption, and, yes, there were different assumptions that could have been made, yes.

Q. What they did was, to use sort of the gold standard randomised trial evidence, exclude everything else and reach an assumption that you disagree with, but then apply their expert clinical judgment to reach a view about the ranking of phenytoin and that is one route through, is it not?

A. Yes.

Q. Just one other document I want to show you on this. Could we turn to {XF3/27/1}. It is an article called "Pharmacoeconomics: NICE's approach to decision-making", and it is by Rawlins et al which we looked at earlier.

If we could go to a different part of it, could we go to page {XF3/27/2}, please, it is under the heading on the left-hand side this one, the red heading "Cost-effectiveness" in red, and could I ask you to read the two paragraphs under that heading. (Pause)

We take three points from this passage and I just want to see if you agree with them.

First: economic modelling in respect of QALY requires judgment by modelers and decision-makers on multiple factors including cost and the benefits in terms of health states; do you accept that?

A. I accept that.

Q. Second, this gives rise to considerable uncertainty both qualitatively and quantitatively; do you accept that?

A. I accept that.

Q. And third, NICE in its work takes into account the views of clinical experts and patients in order to decide the best estimates and then the decision of NICE's own advisory boards are critical. That is how NICE --

A. I accept that, yes.

Q. Of course, as we discussed earlier when it comes to your modelling, none of this process has been completed of NICE reviewing it and coming to its own views?

A. Correct, this has not been reviewed by NICE.

Q. Can we now go to paragraph 28 of your second report which is at {XE3/2/11}. Can I ask everyone to read paragraph 28. (Pause)

The bit towards the end is that your finding of similarity between the comparators supports your primary conclusion that at a minimum, phenytoin provides value comparable to other adjunct therapies at its new price. That is your position, is it not?

A. Correct.

Q. Now, I understand you to accept, Dr Skedgel, from what we discussed earlier that NICE does not just consider the outcome of this evaluation, but it would also consider uncertainty as part of its decision-making.

A. Correct.

Q. Can we bring up on the screen figure 7 of your second report which is at -- and this is for the left-hand side of the screen -- {XE3/2/29}. Can we then go to paragraph 53 of Professor McGuire's position paper which is at {XE6/6/18}.

Sorry, I think I might have the wrong figure, but when we go to Professor McGuire's position paper

I should get told where the right one is. No, it is the right one, sorry.

Can I ask everyone to read paragraph 53. (Pause)

Now, I want to focus on the last two sentences of that paragraph and where Professor McGuire outlines the alternative reading of your results.

Do you agree with Professor McGuire that it is equally right to say there is a 50% error probability that phenytoin is cost effective at this level?

A. Yes, in the nature that that is how a statistical distribution works. What I am reporting is the expected value of that distribution and more or less by definition that expected value is at 50%. To the extent that the mean and the median are close to each other, that would be 50%, yes.

Q. We have agreed, I think, Dr Skedgel, that NICE would be interested in the degree of uncertainty around there?

A. Yes.

PROFESSOR WATERSON: Would normal distributions be usual here?

A. No, in fact you would tend to see more of a right-skewed distribution.

PROFESSOR WATERSON: Right.

A. In fact, one of the textbooks that I reference have a case study where exactly that happens, that the

deterministic number is more favourable than the probabilistic number, kind of what has been adhered to.

PROFESSOR WATERSON: Mean and median would typically differ?

A. Yes, yes.

THE PRESIDENT: Why is that? Why does one have an asymmetric distribution?

A. Because biologically there is a zero point: you can gain nothing, you can die.

THE PRESIDENT: Sorry, I missed that.

A. Sorry, there is a sort of biological hard cut-off to the left where you --

PROFESSOR WATERSON: A truncation.

A. Yes, whereas you could gain a great deal of QALYs or life years on the right-hand side, so it tends to shift the benefit towards the right.

THE PRESIDENT: Yes, thank you.

MS MORRISON: I am sure everyone will be very pleased to hear that I am moving to my final topic, so I think I will finish in good time.

THE PRESIDENT: I am grateful.

MS MORRISON: Can I now discuss the comparison you make between the average daily costs of the 2012 third-line anti-seizure medications that you consider in figure 3 of your first report. Could we go to {XE3/1/22}, and could we bring that up for the full page, please.

Now in this diagram and in your discussion of the comparison of the prices you do not make any distinction between patented and generic products, do you?

A. No.

Q. You therefore make also no distinction between branded and unbranded drugs?

A. Correct.

Q. Are you aware, Dr Skedgel, that in 2012 where you have taken your pricing data from, a number of these drugs were still on-patent, in fact four of them?

A. I was not aware.

Q. I will take you to those documents, then. The first one is pregabalin. If we can go to {XN3/22.1/4}. This is actually from a judgment, but we are not going to the law, we are going to one paragraph on the facts.

If we could look at paragraph 4 and just read that.

(Pause)

This one, it was patented, it expired in 2013, but the prices that you have taken were from the patented period.

A. Okay.

Q. Then if we could look at perampanel which is at {XO/26/33}. This notes under the "Recommendation" heading --

A. Sorry, I have lost my screen.

THE PRESIDENT: Well, Ms Morrison, I am wondering, clearly Dr Skedgel cannot tell us out of his own knowledge, it is well outside his expertise, whether something is on or off-patent. It does seem to me that given this is something which is readily available from the register of patents that that can be agreed between the parties when something came off-patent and when it did not, and I am quite sure that Dr Skedgel will accept the outcome of that approach.

MS MORRISON: The only other document I was going to show him was an extract from his price cost data which actually does have a classification of the prices being branded and generics, but given that I was just going to show him the document and say there are branded and generic pricing.

THE PRESIDENT: I think if Dr Skedgel can add value from his expertise --

MS MORRISON: I don't think so, it was just to show him it and to confirm it, but I think we can probably just take it from the data as it reads, so therefore that is actually the end of my questioning.

Questions by THE TRIBUNAL

PROFESSOR WATERSON: Just coming back on our discussion about the mean versus the median, my understanding is that you take the mean -- is that right? -- but it would

also be possible to focus on the median and the median within the distribution would be lower than the mean because of the skew?

A. Yes. This is going to the point of the ICER versus the net marginal benefit.

PROFESSOR WATERSON: Yes.

A. The mean -- the expected value for my ICER is the mean of each distribution, whereas the 50% cost-effectiveness acceptability curve is the median of the distribution of net monetary benefit.

PROFESSOR WATERSON: Right.

A. Which, as you say, is probably lower than the mean of that distribution.

PROFESSOR WATERSON: Thank you.

THE PRESIDENT: Mr O'Donoghue.

MR O'DONOGHUE: I have less than a handful of points.

Re-examination by MR O'DONOGHUE

MR O'DONOGHUE: Dr Skedgel, you were asked at some length about the distinction between technology appraisals and guidelines, and you said in terms of the cost effectiveness methodology it is essentially common as between those two.

A. Yes, that is my interpretation.

Q. Can I just give you two references for that. The first is your first report at {XE3/1/10}, paragraph --

A. The screen has gone blank. (Pause)
Q. Dr Skedgel, are we live?
A. Yes.
Q. Excellent. So you see paragraph 41 which you were taken to, and you see in the third line -- or second line:

"... to the extent practicable, the approach that would be taken by NIC, had it been conducting an appraisal of phenytoin in a technology assessment or as part of a clinical guideline ..."

Again, it may be obvious, but can you explain to the Tribunal why you say a technology assessment or as part of a guideline?

A. Because, as I laid out, from my perspective as a health economist and particularly as a health economics modeler, I would not approach my model in any different way for either approach, either programme.
Q. Thank you. Finally on this topic, can we look at what Mr Hawkins says. That is at {XC1/6.1/5}. You see the third sentence:

"In principle, while there are some differences in methodology for consideration cost effectiveness between the guidelines and TA methods manuals, I agree these should not make a difference in this particular case."

Then he goes on to make the point about the impact on pricing.

Do you agree with Mr Hawkins' assessment?

A. Yes.

Q. Second, you were asked about the non-inclusion of Cramer, and you made the point that the efficacy in Cramer, such that it was, was 28% compared to your 6.9%. Now, it may be unfair to ask you on the hoof, but had you adopted the Cramer estimate of efficacy, what impact, at least in ballpark terms, might that have had on your results?

A. I do not think I can say what the impact on the ICER would be, but given solely the fact that that is a bigger number than -- 28% is a bigger number than 6.8%, it could only have improved my estimate of the cost per QALY. It would have increased the denominator in my ICER calculation and led to a more favourable ICER.

Q. Thank you. And again, I think you said the primary reason you did not include Cramer was because from your perspective it focused on quality of life?

A. Yes, well, it focused on quality of life, it did not specifically focus on efficacy, but more pragmatically it just -- there was no way for me to incorporate the number that Cramer was reporting into the model that I was building.

Q. Because of the fusion of partial and complete?

A. Yes, that it did not distinguish partial and complete response.

Q. Now, you were asked quite a bit about pricing being at or just above £20,000. Can we first of all go to your teach-in, it is at {XE7/8/28}. So these are the different price permutations you considered. Are you able to briefly run the Tribunal through the numbers you have considered on this table?

A. In the sense of where the prices -- what the prices represent or what their impact on --

Q. Yes, in basic terms what they represent.

A. As I understand, £67.50 was the price at the heart of the proceedings here, that was the price in 2012 -- 2012. I understand the price decreased in May 2014 to £54 a pack. Again, by the same mathematical logic, a larger number in the denominator or a smaller number in the numerator lead to a more favourable cost per QALY gained. So £54, as I understand, is the capsule drug tariff price in 2014. There are prices for Flynn of £48.95, there is Pfizer's supply price in the last quarter of 2012 is £40 and then the CMA estimate of cost plus, I understand, is £4.90.

I think what is somewhat notable in this is the cost per QALY gained is relatively insensitive to the price itself which almost counterintuitively suggests the

value is relatively insensitive to the price in a way that is slightly surprising to me as a health economist and a modeler. I am somewhat surprised by how insensitive, and I noted in my report that part of it is the relatively low response weight, at 6% response rate 94% of people are not responding to these medicines, and, therefore, most of the costs and the outcomes in the model are being driven by the people who have discontinued treatment.

So that puts a lot more weight on a common pool of costs and outcomes. As part of my model, once you have failed one of the specific treatments, I moved you in the model to a virtual pool where I just took the average of everything on the assumption that you would churn through the other third line options. I assigned an average price to avoid making any judgment about what you would move to after perhaps your -- the first third-line treatment that you attempted.

So in that sense, everyone is being 94% plus or minus depending on the response rate of the individual product are all being assigned the same cost and the same health outcomes once they have failed or once they have failed to respond on one of the active treatments.

So to me, that is the explanation for why cost per QALY is relatively insensitive to the price of the

product itself.

Q. Thank you. My penultimate question, again sticking with the £20,000 figure, you were taken to Rawlins, it is {XF3/27/2}, and you will recall, Dr Skedgel, on the bottom right you were taken through points 1 to 4, but you were not shown the paragraph underneath. Can I ask you to read that and add any commentary you think is appropriate. (Pause)

A. Yes, I think this is consistent with a comment that I made in my original report that NICE is quite vague about where these numbers have come from and have always avoided -- I think the word "hard-edged" has been used. They always avoid implying there is a hard edge to this. There is a change in the probability of approval or rejection at different points along this curve, but it is not a right angle: you will be accepted here and you will not be accepted there.

Q. Do you agree with the point in the fourth line:

"NICE's advisory bodies would be unlikely to reject, as cost ineffective, an intervention [at less than] £20,000 per QALY ..."

Is that consistent with your experience?

A. Yes. The probability of rejection is relatively low below £20,000, yes.

Q. My final point I want to go back to something you were

asked about societal valuations. I want to show you something that Professor McGuire said on that topic yesterday. It is at {Day14LH1/60:14}.

Do you see the President's question?

A. Yes.

Q. Down to 22, if you can read that. Let us know if you agree or disagree.

A. Sorry, this is my testimony.

Q. It is your teach-in.

A. I agree.

Q. Well, the point I am putting to you, is it consistent with what you gave in evidence this morning?

A. Yes.

MR O'DONOGHUE: Thank you. Sir, I have no further questions in re-examination.

THE PRESIDENT: Thank you very much, Dr Skedgel. We are very grateful for your help and you are released from the witness box with our thanks.

MR O'DONOGHUE: Sir, we now have Professor McGuire. I am in your hands as to whether --

THE PRESIDENT: Yes, I have one point of clarification for Ms Morrison, and then I suggest we rise and resume at probably 1.55 to start with the next witness.

Just for my clarity, Ms Morrison, there was a NICE 2022 guidance that we have heard a great deal about

which is outside our relevant period and so on that basis of less relevance than other guidance, and phenytoin I understand failed that guidance in the sense that it was no longer recommended.

MS MORRISON: Yes.

THE PRESIDENT: Does that mean --

MR O'DONOGHUE: Sir, no, it was recommended.

MS MORRISON: No, sir, it was recommended. It was of course recommended, everyone agrees it was third-line recommended, but it failed the cost effectiveness analysis in that it was negative. It was a minus number in the --

THE PRESIDENT: I see, right. So it failed cost effectiveness but passed --

MR O'DONOGHUE: Well, sir, there is quite a lot to unpack there. I am not going to --

THE PRESIDENT: Well, who is doing the unpacking?

MR O'DONOGHUE: Well, sir, one needs to be careful with words, but first of all this was not cross-examined on, which is fair enough, but --

MS MORRISON: I did actually put that it failed at a lower cost, so I did.

THE PRESIDENT: Look, I do not care who put and who did not put it. I just want to understand what the position is.

MR O'DONOGHUE: Sir, let me explain briefly what we say the

position is.

The ultimate recommendation was that it be continued to be recommended as a third-line drug.

THE PRESIDENT: Right.

MR O'DONOGHUE: In terms of the economic assessment, the only reason it failed that economic assessment was based on a rigid adherence to a principle that, unless there were randomised clinical trials at the third line in relation to phenytoin, they would not accept anything less than that as the best evidence of effectiveness.

Now, because of that assumption of principle, they assumed that phenytoin was no more effective than a placebo, but it was simply an assumption, and that assumption then drives the economic assessment, and to that extent only there is a cross against phenytoin, but it is not the case that, having considered positive evidence of efficacy, they then concluded based on the clinical data that phenytoin was not cost effective. There was an absence of evidence rather than positive conclusion, if that makes sense.

MS MORRISON: Sir, if I can say, that was just a longer explanation of precisely what I was saying, is that phenytoin was recommended as a third-line drug, we do not dispute that. NICE's economic model gave rise to a negative result, but they reached a positive

recommendation in the end, and I did in fact put that to Dr Skedgel that it was found to be below at a lower cost.

THE PRESIDENT: Slow down. The reason I am asking for this is I am not actually that worried about the economic analysis in terms of why it failed or why it did not. What I am interested in asking -- and it may go nowhere -- but what was the reason for overriding the negative economic analysis, for whatever reason that may have existed?

MR O'DONOGHUE: Sir, I put that to Mr Hawkins --

THE PRESIDENT: Well, let us go first to Ms Morrison and then I will hear from you, Mr O'Donoghue.

MS MORRISON: Sir, our understanding is basically what is on the page from NICE and as Mr Hawkins has explained. Ultimately NICE has its model designed for it in conjunction with somebody like Mr Hawkins. He was very clear that he does not decide how the model is designed. It is then for the committee to go away. As I discussed with Dr Skedgel, the committee goes away and makes its expert judgment, not just based on the model but on its expertise and material before it, and it obviously came to the conclusion that phenytoin was a drug that it wanted to recommend and therefore it was effective. But I think there are two things going on, sir: there is

what you want to do in your economic model and the decision you make.

THE PRESIDENT: You said "therefore effective". That is a hypothesis.

MS MORRISON: Sir, I think everyone accepts that by dint of the fact it was recommended there was some judgment that it was effective because they would not recommend an ineffective drug, and the CMA takes no position that phenytoin is ineffective in general, we accept it is effective for some people, we have set that out.

THE PRESIDENT: The only reason I am asking -- and I am sorry for having caused such a ruffling of feathers -- is this: we do not know whether it was continuity of supply to the existing patient pool that was the factor that may or may not have been in the committee's mind when they decided that phenytoin should continue.

MS MORRISON: I see, sir. To that extent it is a black box because we do not know what the clinical expertise was that was being taken into account, I fully accept that, sir.

THE PRESIDENT: That is very helpful. Anything more to add on that, Mr O'Donoghue?

MR O'DONOGHUE: Just to give you the reference, sir, which I was over-enthusiastic about, I apologise. I put this to Mr Hawkins yesterday, so it is at {Day14LH1/180:5}

and following, this is yesterday, page 180, starting at line 5.

So what I put to him was that the cost effectiveness was ultimately overturned by the committee's recommendation, you will see what I put, and then he says at 16:

"I think that is reasonable."

So we know it was overturned, it seems with clinical reasons. Whether that was specifically in relation to continuity of supply, narrow therapeutic index or something at a higher level of abstraction, I think we do not know concretely, but it may be something we could investigate further.

THE PRESIDENT: I am not sure you can because it would require evidence from the committee in question.

MR O'DONOGHUE: Indeed.

THE PRESIDENT: That was the only reason I was asking it. I wanted to know whether there was any material that fed into the continuity of supply question and the answer is we do not know.

MR O'DONOGHUE: Yes. We have checked, we have not found anything to date. We will obviously keep checking.

THE PRESIDENT: Thank you.

MS MORRISON: Sir, that was also my understanding. There is not that sort of unpacking, and there is just

a judgment.

THE PRESIDENT: Thank you very much.

We will resume at 2.00.

(12.57 pm)

(The short adjournment)

(2.00 pm)

PROFESSOR ALISTAIR MCGUIRE (recalled)

MS MORRISON: If I could call Professor McGuire forward.

THE PRESIDENT: Thank you very much.

MS MORRISON: There was a discussion yesterday of slide 7 in Professor's McGuire's pack and he has made some amendments in light of the discussions he had with the Tribunal.

THE PRESIDENT: Oh right, that is helpful.

MS MORRISON: So he is just going to explain the changes that he has made when he comes up.

THE PRESIDENT: Professor McGuire, welcome back, do sit down, make yourself comfortable. Your reports are in evidence, they will not be put to you again, you are still under oath, you will not be re-sworn.

Before I hand you over to -- Mr Brealey, are you doing the cross-examination?

MR O'DONOGHUE: I am afraid it is me.

THE PRESIDENT: Oh, very good. I was duped by Mr Brealey being on his feet.

MR O'DONOGHUE: Sorry, you sounded optimistic.

THE PRESIDENT: Dare I say it that you are all substitutable?

MR O'DONOGHUE: Not perfectly so.

MS MORRISON: That makes me sad, sir.

I just ask Professor McGuire to explain the changes he has made.

THE PRESIDENT: Of course.

A. Sir, I am sorry for this, but in trying to reduce complexity down to a small schema, maybe I did not get some of the points across.

So there are three basic changes to this slide. One is HTA process and I think we had branded drug pricing above. It should be patented drug pricing because there are, of course, branded drugs which I kind of slipped over in my explanation, I think, and there is a change to the first box in the top line which says -- which essentially tries to say that these patented drugs will go into the drug tariff of course, they do go into the drug tariff, and maybe that is where your questioning came from President, yesterday.

Then there is an additional box on the bottom row saying that branded generics, which are of course priced through the PPRS and VPAS mechanism, they nonetheless could go into the generic -- into the discussion of NICE

as a generic drug through their guidelines process.

In other words, one of the take-homes from this change is that the branded generics -- I do not know of any branded generic -- and this may be ignorance -- which has gone through an HTA process assessment. I think there are only new patented drugs which have done so.

Then the last point, which I think is where we had some discussion, was I said that NHS purchasers and in particular CCGs have to take the drug tariff price as given, that applies to branded generics and generics, but there may be negotiation over the patented list price, and that is really why it is an amendment, to try to clarify that.

THE PRESIDENT: Thank you very much, Professor, much obliged to you.

Just on that, Mr O'Donoghue -- and no doubt you may have or may not have some questions on this -- but just to assist everyone in terms of how we are going to approach the structure of the market of the NHS, we are not going to be taking any single witness's version as gospel. We are probably going to try and start with the black letter law and then move into the practice, deploying all of the evidence that is going on.

So if you are going to cross-examine on this,

I would not worry too much about the dots and the commas. I would worry about the broad picture because that is where we are going to start and we will be looking at what everyone has said, including the two medical experts who did give some interesting and helpful evidence on this as well.

MR O'DONOGHUE: Well, sir, that is extremely helpful, and I can assure you I have plenty of other things to worry about.

Cross-examination by MR O'DONOGHUE

MR O'DONOGHUE: Professor McGuire, good afternoon.

A. Good afternoon.

Q. Now, can I start with OHE. You would accept that OHE is a highly respected health economics consultancy, it is one of the oldest in the world as I understand it?

A. I would have to, my wife works there.

Q. Ah, so we have at least avoided an awkward discussion in the McGuire household?

A. Yes.

Q. Thank you. As I understand it you have in the last collaborated with OHE on various projects; is that correct?

A. Yes.

Q. Now, Dr Skedgel indicated that he has been directly involved in building I think he said around 30 economic

models across a range of different illnesses, and it is not, obviously, a competition, but for perspective, how many models have you yourself directly built?

A. At least a dozen, I would say. I am going back into the reaches of my memory now. I would say at least a dozen. Less than 20, maybe somewhere between a dozen and 20.

Q. Were these for manufacturers?

A. A minority were, yes.

Q. For NICE?

A. No, none for NICE as a manufacturer submission, no.

Q. So you have never built a model for NICE?

A. No, that is not what I said. I said I have never built a manufacturer's submission as a model for a submission to NICE; I have inputted into NICE guidelines and as the guidelines' developers have tried to build a model for the guidelines, I have inputted into that. I would not claim authorship or claim propriety over that, though.

Q. So is it fair to say you have not yourself directly built a model, but you have given some input into models built by other people?

A. No, not precisely. I have built models, but as an academic; I have not built any models for NICE per se.

Q. Is that because, as I understand it, you are a full-time academic?

A. I hope so, yes. Yes.

Q. Now, your work in building models, did you not think it was appropriate, given the trenchant criticisms you make of Dr Skedgel's model, to be clear as to your own experience of building models? Did you not think that would be helpful?

A. Sorry, I missed point there. My own experience would be helpful for what purpose?

Q. Well, you do not indicate in your report or your position paper your experience of building health economics models. Did you not think that would have been helpful?

A. I do not think it would be unhelpful, that is certainly true; whether it would be helpful to give my experience in building models, possibly. Could I just also say that I am not -- the trenchant criticism of Dr Skedgel's model is not with respect to the intrinsic quality of the model, as I said yesterday, it is about my instructions were to assess that model with regards to the NICE methodology.

Q. Well, you do not pull your punches, you say NICE would have rejected it?

A. I believe they would have given it a very low quality standing and rejected it, yes.

Q. That is not trenchant, in your opinion?

A. No.

Q. Okay, well let us move on. Now, as I understand it you have three overarching criticisms of Dr Skedgel's report. The first is you say the QALY concept is not informative for assessing the economic value of a pharmaceutical product under competition law, and you say, and I quote:

"QALY analysis does not assess economic value as I understand it is used in a legal sense."

Are you happy with that?

A. Yes.

Q. The second criticism you make is that you say Dr Skedgel's model is not robust and here you challenge his core assumptions and make some criticisms around what you say is uncertainty in his model.

A. Yes.

Q. But you at least accept that Dr Skedgel has been transparent in setting out his methodology and assumptions?

A. Yes.

Q. So that is the second point.

Now, pausing there, you do not put forward any competing model of your own. You criticise Dr Skedgel, his model and assumptions, but you do not offer any alternative model or indeed assumptions; it is a destructive or negative exercise only.

A. My instructions were to assess Dr Skedgel's model against the methodology of NICE as used by NICE. I was not asked to put forward an alternative, I was not asked to suggest alternatives to his own model, it was merely to assess whether his model stood up to the standard of NICE, and, as we have agreed --

Q. So the answer to my question is "yes"?

A. Yes, that is certainly true, yes. It was not under my instruction, yes.

Q. Well, there was nothing preventing you -- let us take the assumptions. There was nothing preventing you from putting forward an alternative assumption, was there?

A. No, just the opportunity cost of time, yes. Nothing other than that, yes.

Q. Well, you have had a year.

A. I do do other things in my academic full-time work.

Q. All right, let us move on. So that is the two criticisms.

The final point you make is a distinction, you say, between the technology appraisal process and the guideline process, and you make the point here that whilst a technology appraisal might play a role in pricing negotiations, that is not true of the guideline process, particularly for generic prices?

A. Yes, that is true. I quibble over the term

"negotiations", but they may for the HTA, for patented drugs, it may be that there are negotiations over price and price is an input into the cost effectiveness analysis that NICE undertakes.

Q. Well, we will come on to all this in detail, do not worry about that, I am trying to understand what are your core criticisms to tee up where we disagree.

Now, what I want to do for the rest of the afternoon is to cover these three points with you in some detail and then deal with a handful of shorter discrete points.

Now, can we start with the question of economic value. Now, we can presumably agree that you are not a competition lawyer?

A. You do not need a presumption for that, I am not.

Q. And you are not a competition law economist?

A. No.

Q. You cannot therefore give expert evidence on the concept of economic value under competition law and economics; that is not within your expertise?

A. Yes.

Q. Your area of expertise is health economics, that is the scope of your instructions.

A. Yes.

Q. Now, before we get on to some of the points, the statements you make about economic value and QALYs,

can I just deal with one discrete point. You raise in your position paper something called distinctive value. Do you remember that?

A. Mm-hm.

Q. Now, if we can just bring this up in your position paper, it is at {XE6/6/1} and paragraph 34 which I think is on page {XE6/6/11}. Do you see about two-thirds of the way down you say and I quote:

"... QALY analysis of a generic drug ... cannot tell you whether or not the price for a generic drug is justified by, for example, 'distinctive value' (which is unlikely for a generic drug in any event) or whether it is the product of 'market power', as the Tribunal discussed in *Hydro*."

Now, you do not mention the concept of distinctive value in your report, and surely if as a matter of health economics this concept was important, you would have mentioned it in your report; is that fair?

A. Yes, to put it in some context, the *Hydrocortisone* Decision came out in between my report and the position paper --

Q. Yes.

A. -- and that is I think why I am referring to it there rather than earlier.

Q. Yes, you refer to *Hydro*, as you say, that is fair.

A. Yes.
Q. But you do not refer to your instructions in relation to that judgment, I have not seen those set out in your position paper or anywhere else. What is your understanding of the concept of distinctive value as set out in that judgment? What were you instructed?
A. So the instructions were slightly -- they are set out, my instructions, I think, in the first paper, my first paper which is submitted.
Q. Yes, but that did not include *Hydro* as you told us.
A. Pardon?
Q. That could not have included *Hydrocortisone*, as you told us.
A. No, that is true, that is certainly true.
Q. So what were your instructions on *Hydrocortisone*?
A. In terms of this particular point, I was not instructed to do anything other than read the *Hydrocortisone* paper.
Q. Have you actually read the judgment?
A. Yes.
Q. Can we look at what Ms Webster says about this? She is the CMA's expert economist. It is at {XE7/4/8}.

These are her teach-in slides, and you will see under (b) she refers to case 2:

"... supplying a differentiated product ... that brings additional value to customers."

Then if you read down under 4:

"In my view, it would be reasonable to say that [the] investment by the Parties in ensuring the reliability of supply of Capsules, given the need for Continuity of Supply, may be of some economic value."

Now, if we go back to your position paper, the previous document, please {XE6/6/11}, you seem to disagree with Ms Webster. Is that true?

A. So I was not mentioning continuity of supply, that is certainly true. By distinctive value if that is the point you are trying to get me to go back to --

Q. Yes.

A. -- I think I would agree that there is, to my mind, no product differentiation with regards to a generic drug. That is the point I am trying to make.

Q. But the point she is making, which you are avoiding, she says because of continuity of supply there is distinctive value, it is case 2. Do you agree or disagree with that?

A. No, I agree that is what she is saying.

Q. Do you agree with it?

A. I am saying I am not mentioning continuity of supply here, and I am not trying to make a point about continuity of supply. What I am doing is saying distinctive value, as I understood it, and not being

a competition lawyer or competition economist, as I understood it, distinctive value would refer to the product characteristics, and if you have a generic product, to my mind, the characteristics would not be differentiated across the generic product because a generic product would not be able to get on to the market unless it had been licensed as a generic.

Q. But you say in the closed brackets:

"...(which is unlikely for a generic ... in any event)..."

Are you saying that no generic drug could ever have distinctive value?

A. My understanding would be that if you are allowed to manufacture and license a generic drug in the UK, you should not be able to distinguish that drug from any other generic drug in terms of its compound composition.

Now, if there is an additional point to be made about continuity of supply, I think that probably refers to incumbent patients using the drug, and this response is in response to Dr Skedgel's model which is about incident patients.

Incident patients are not already on the drug, but are new patients to the treatment, and as new patients to the treatment, if they were offered a generic drug, I would say there should not be any distinguishable

characteristics from that set of generic drugs, and that would be my elaboration on this point.

Q. So to be clear, and I am going to move on --

PROFESSOR WATERSON: Can I just check on that? What you are saying is that, for example, if someone starts on phenytoin, they might be started on the capsule or the tablet, they might be started on different manufacturers' brands of either one or the other?

A. Precisely, and that is exactly the starting point of Dr Skedgel's economic model.

PROFESSOR WATERSON: Thank you.

MR O'DONOGHUE: Let me ask one final question and then I will move on.

If there is continuity of supply imposed by the MHRA in respect of legacy or what you call incumbent patients, do you agree or disagree that involves distinctive value?

A. I would say that if there is a continuity of supply element associated with a particular drug, it would obviously reflect both distinctive value but also some form of market monopoly because if there is a distinctive element to it, then there would have to be some reason why the patient is retained on it.

Q. It could simply be the drug is extremely valuable for those patients and saves their lives; what has that got

to do with monopoly?

A. Well, that is where the idea to me of distinctive value comes in, that if it is a true generic and it has a licence as a generic, as Professor Waterson has just pointed out, if they were going on to treatment they could be on any generic, and that is the point I was trying to make in my position paper.

Q. Well, let us move on. Let me just put one final point in this, I am going round in circles. In 2013 the MHRA in category 1 listed only four AEDs, including phenytoin, in terms of continuity of supply.

Do you think that categorisation by the MHRA, which was independent of any question of monopoly, amounts to distinctive value or not?

A. This is a new question to me, and I would say yes, but that is not what I was asked to do in criticising or not criticising but assessing Dr Skedgel's model with regards to NICE methodology, but as you have put the question to me now, yes, it is a distinctive characteristic if there is a continuity of supply associated with a particular generic drug, but that is completely outside of my remit and I am sorry if I misled you in referring to distinctive value in my position paper, in thinking that I was talking about continuity of supply.

Q. Okay, well let us move on, thank you. Let us go back to economic value and what you say.

If we can bring up your first report, it is at {XE3/3/4}, please.

In your report, you make two basic points on economic value. You see in the footnote, if that can be blown up, please, you say:

"... it has been explained to me as 'what it is that users and customers value and will reasonably pay' for the product in issue."

Do you see that?

A. Yes.

Q. So you emphasise the value to users and customers; do you see that?

A. Yes.

Q. The second point you make in paragraph 14 just above that, you say, again, you understand, you have been instructed that economic value in competition law is about what the price would be under normal competitive conditions, over the page, please. And you say:

"Instead, product price is a predetermined input to cost effectiveness (QALY) analysis."

So the second key point you make is the concept of normal competition.

Happy with that?

A. Yes. Could we go back a page? I did not see because of the --

Q. Yes, by all means.

A. Where it says "a legal sense", that is where it is referring to footnote 2. I cannot see what goes beyond that.

Q. Oh yes, if we scroll up.

A. Just to make clear. Yes, okay.

Q. Under (c), have you got that?

A. Yes, thank you.

Q. Okay. So you have these two what I would call criteria, so let us start with the first one: what users and customers value and would reasonably pay.

Now, let us look at the word "user". It would be fair to characterise the patient as the user, would it not? They are, after all, the person consuming or using the medicine?

A. Yes.

Q. From the user's perspective, all they care about is getting a therapeutically useful medicine with minimal or no side effects. They do not care or even necessarily know what the medicine costs.

Do you agree with that?

A. Yes.

Q. So it is therapeutic utility or efficacy, correct, from

their perspective?

A. So, yes, that is what they value, yes.

Q. Yes. Now, the QALY analysis includes as one of its critical components an assessment of the therapeutic efficacy of the drug?

A. Yes.

Q. So if, as you say, economic value means value to the user, that must include the therapeutic benefit to the patient?

A. Yes.

Q. And, as you agreed, that is part of the QALY assessment?

A. Yes.

Q. So at least from this perspective, the QALY assessment is consistent with your understanding of economic value in your report?

A. So if we think of a QALY analysis as a cost per QALY analysis and think of the threshold that the NICE and the NHS is using to value that QALY, then that would be the NHS's willingness to pay up to that threshold based on the opportunity cost of other NHS treatments for that QALY.

As an individual patient, you may -- in other words the individual consumer surplus, may or may not be the same as that QALY value that is given to it by the NHS.

Q. Well, I think we are running ahead of ourselves. I am

putting a very simple point to you which I think you agree with, which is from the user perspective, the patient, therapeutic benefit is their primary concern, and therapeutic efficacy or benefit is part of QALY?

A. It is part of the QALY, yes.

Q. Yes. Now, were you aware that the CMA was instructed by this Tribunal to gather evidence on therapeutic value in its judgment in 2018? Let us have a look at that. It is at {XN1/2/133}.

Do you see, Professor, at 419:

"... our finding is that the Decision was defective in its treatment of the economic value that may be derived from patient benefit. Placing a precise monetary value on patient benefit is not straightforward but it appears to us that a qualitative assessment would be possible and should have been attempted by the CMA rather than simply assessing this value as nil."

So the CMA was instructed by the Tribunal to go back and gather the evidence on therapeutic benefits as part of economic value; do you see that?

A. Yes.

Q. Now, the QALY evidence includes detailed evidence on clinical effectiveness, I think you have just agreed with that. Yes?

A. Yes, yes, sorry.

Q. So again, from this perspective, there is no inconsistency between how you define economic value in your report and the QALY evidence?
A. Therapeutic value is part of the QALY value, yes.
Q. Yes.
A. Yes.
Q. Indeed, I would suggest it goes further than this: the QALY provides a very useful proxy or measurement of this aspect of economic value.
A. Again, I would say that it is not necessarily the case that the patient's consumer surplus or value derived directly from a (inaudible).
Q. We will come on to that. Again, we are in the foothills.
A. Yes.
Q. The simple point I am putting to you, in the context of QALY, NICE and/or the manufacturers will go out and gather as much clinical evidence on efficacy as they can lay their hands on: the RCTs, observational studies and so on?
A. Yes.
Q. So they are looking at therapeutic benefit.
A. Yes.
Q. So that is your first component.
Now can we look at your second component which is,

and I quote:

"... what customers value and would reasonably pay for the product at issue."

Do you remember that in the footnote?

A. Yes.

Q. So we are moving from users to customers.

Now, you would agree that one could consider the NHS or the Department of Health and Social Care as a customer for these purposes since they are the entity paying for the drugs or underwriting the whole system. They are, in effect, a purchaser. The patient pays zero save perhaps for a prescription charge if applicable. Do you agree with that?

A. So you are making a distinction between users and consumers now?

Q. Customers.

A. Customers. I would say that the NHS reimburses for the purchase, so if that is a definition of customer, yes.

Q. So you accept they are a customer for these purposes?

A. If -- yes, if -- yes. They do not gain the therapeutic value themselves, obviously, but they are purchasers and reimbursers for the drug, yes.

Q. They are footing the bill?

A. They are footing the bill, yes.

Q. Can we look at what the CMA says about this because

I think you are in violent agreement. If we go to the Decision at {XA1/2/60} please, and you will see, Professor, at E.94 they say:

"... the Court of Appeal noted that economic value is what 'users and customers value and will reasonably pay for.' In this case, the end customers are the CCGs and the NHS, and the users (or consumers) are [the] patients."

A. Yes.

Q. So I think everybody agrees about that.

Now, again focusing on the NHS as customer, do you therefore accept that it is reasonable to consider what value the NHS as the customer places on the product in question when asking about its economic value?

A. Yes.

Q. Now, again, can we go back to the 2018 judgment just to anchor ourselves on why we are back here on this point. It is at {XN1/2/67}, please.

Professor, it is at 204. Do you see about a third of the way down:

"... the DH, whether through the NHS or the CCGs, was by far the largest purchaser of pharmaceutical products in the UK, and indeed was effectively the only end customer for [the] Pfizer-Flynn Capsules ..."

Do you see that?

A. Mm-hm. Yes.

Q. Now, I just want to show you one case, I am not going to ask you a legal question, and then we will come back to economic value in the present context. If we can go to the authorities at {XN3/10/35}, please. This, Professor, is case called Attheraces about race data and their commercial exploitation. If I can ask you -- well, let us read it together. You see in 186, Professor, it says:

"Mr Roth's --"

Do you see second contention and all that? It says:

"Economic value looks [at] the demand side rather than the supply side. It means the value of the customer."

Do you see the last two sentences?

A. Yes, just give me a moment to read it, please.

Q. Yes, please do. (Pause)

A. Yes.

Q. Then Professor you will see at 189, the second question which is, and so on:

"... the economic value of the product was a different concept from its cost, as it reflects [the] revenue-earning potential to the person who acquires it."

Then you will see that somebody paid hundreds of

millions of pounds for the data in question.

Then if we jump forward to paragraph 203 {XN3/10/38}. This is the court's ruling:

"... [the judge] erred in holding ... the charges proposed by BHB were excessive and unfair. We are in broad agreement with Mr Roth's submissions criticising the judge's approach to the issue of excessive and unfair pricing of the pre-race data."

So that is the points we just saw.

Then if we go to the end at 218 {XN3/10/41}, you will see the second sentence:

"In particular he [the judge] was wrong to reject BHB's contention on the relevance of the value of the pre-race data to ATR in determining the economic value of the pre-race data and whether the charges specified by BHB were excessive and unfair."

So the basic point here is that economic value includes the value of the product to the customer, and in this case it was the fact that the pre-race data allowed Attheraces to make higher profits in its market by commercialising the pre-race data in question. So that is the economic value of the input in terms of its revenue-generating potential.

Now, I want to look at the other side of the coin which is a situation where the product purchased allows

the purchaser to achieve substantial cost savings as opposed to generate substantial profits. Are you with me?

A. Yes.

Q. Now, in the context of the NHS, the majority of the costs of epilepsy are not the costs of acquiring the drug but the costs if the patient ends up with a seizure and has to transition to a hospital environment. Do you agree with that?

A. Yes.

Q. Let us put some facts and figures on this. If we can start with {XD1/6/1212}, and it is at the bottom of the page.

You see it says:

"The majority of the costs were not associated with the [anti-seizure medication] prescribed, but with later costs for changing treatment or being hospitalised following a seizure. There was also limited difference between the costs of the various treatments. It is therefore likely that of the drugs considered in the model the most clinically effective would also be the most cost effective."

Do you see that?

A. Yes.

Q. None of that is surprising to you?

A. It is not surprising that the hospital costs are larger, no.

Q. Now, let us go on again to put a bit more flesh on these bones. {XF3/68/5}, please. Can we go to the first page just to understand -- {XF3/68/1}. Because Professor, one of the problems, of course, with electronic documents is you get a snippet and if you want to go back to the first page or any other page, just tell me, I want to make sure you have a chance to orient yourself. So this is an NHS PrescQIPP document on AEDs, appropriate switching to generics.

If we can then go forward to page {XF3/68/5}, please. You will see the second line, Professor:

"Avoidance of seizures is the primary goal, while keeping adverse effects to a minimum. When long-term remission has been achieved it becomes important to avoid even a single breakthrough seizure. Just one seizure after a period control can have major implications ... There may even be fatal consequences -- the risk of death in patients with uncontrolled seizures is higher than in seizure-free patients. Therefore considerably more is at stake when treating epilepsy than with many other conditions."

Then at the end:

"The true cost of generic prescribing must also

include the cost of additional visits to a physician or the hospital if the substitution causes problems. Also the cost of treatment failure must be taken into account if a seizure occurs. The cost of one breakthrough seizure in a previously stable patient is so high that it could offset the savings from generics."

Now, again, I do not anticipate you will disagree with any of that.

A. No, no, that is fine, yes.

Q. Now, are you aware, Professor, that when the new price of phenytoin sodium capsules was set there were complaints from CCGs?

A. I am aware, yes.

Q. Can we just look at what the Department said in response. It is at {XG/243}, please.

A. Could I just ask another clarifying question?

Q. Please.

A. By avoidance to seizures, that is complete avoidance, and, as I understand it, that is a very rare outcome, and so the medication as has been assessed by NICE and in other models has focused on greater than 50% reduction in seizures. Obviously, there will be different valuations on --

Q. We are going to come on to that.

A. Right, okay, fine.

Q. One of the criticisms you make of Dr Skedgel's model is the so-called dichotomous outcome assumptions, so I am going to come on to that in some detail.

A. Okay.

Q. So hold that thought.

A. Yes.

Q. So go to {XG/243}. Again, you will see from the heading this is from the Department of Health, and it is addressed to NHS Clinical Commissioners, and you will see the penultimate paragraph. This is from, as you see in the top, Dr Keith Ridge, the chief pharmaceutical officer, who I presume you are aware of, and he says -- so this is in response to the complaints in the CCG:

"The cost of any medicine has to be balanced with the potential additional costs to the NHS through adverse reactions and reduced patient outcomes if supply is interrupted.

"While any price increase is unwelcome, especially at a time of financial restraint ... in the main, the NHS obtained the best value from medicines. For example, we were able to move quickly, earlier this year to reduce the cost of atorvastatin to the NHS when it came off-patent."

I would suggest to you he is basically making the same point which we have seen which is the acquisition

cost of medicine is one thing, but there are other costs which come into the equation?

A. And that is how a cost per QALY is estimated, yes.

Q. Indeed.

A. Yes. You net out the treatment costs, yes.

Q. That is my very point.

A. Yes.

Q. I think following on from what you said -- so you would agree -- I think you said this in your teach-in -- that when NICE does a QALY assessment, it would typically look at the cost savings we just discussed?

A. Yes.

Q. Just to make clear we are in agreement on this, so there is no ambiguity, we can see what Dr Skedgel says in his position paper, it is at {XE6/1/3}, please, and you will see, Professor, paragraph 10 -- why do you not read 10 and the two subparagraphs and then I will ask you a question. (Pause)

A. Yes.

Q. Now, as I understand it from paragraph 46 of your report, you do not actually disagree with anything here in material terms?

A. Yes, that is true. Well, you would have to remind me what I say in 46, but anyway, I do not disagree with this as it stands.

Q. You are happy enough with that?
A. Yes.
Q. Okay, thank you. Now, if, as you say, economic value is what customers value and will reasonably pay for the product at issue, can we agree that it is appropriate to then take account of the substantial benefits to the customer?
A. Yes.
Q. To put it another way, if we left those cost savings and other benefits out of account, that would give a pretty distorted picture of economic value, would it not? You would leave out of account completely the most substantial category of cost savings to the customer, the NHS.
A. Yes, but NICE includes them in their cost per QALY.
Q. Indeed. We agree on that.
A. Yes.
Q. Now, if, as you say, the QALY assessments by NICE include these benefits for the customer, it must follow that the QALY is a useful means of capturing these benefits.
A. Yes.
Q. So again, from the second perspective of the customer -- we have discussed the users -- from the second perspective of the customer, a QALY analysis allows us

to gain some insight into an important aspect of economic value as you have defined it?

A. So I think paragraph 10.2 here is quite useful because it is differentiating between the customer and the user and saying that the user may have less tangible benefits associated with any treatment which are not captured by the QALY, so they are over and above the QALY.

Q. Yes, it is conservative in that respect.

A. There may be, there may be.

Q. Well, they are left out.

A. If they are there, they are left out, yes, and the QALY, from the customer's perspective, tells you something about their valuation in terms of the QALYs being achieved, but it is the QALYs being achieved at the opportunity cost of not treating elsewhere in the NHS, yes.

Q. Well, we will come on to the details, but I am putting a very basic point to you that I think we actually agree, which is the QALY captures the substantial cost savings to the NHS. They are part, on your definition, of economic value: they are a benefit to the customer.

A. Well, just to be precise, the financial savings are captured in the cost part of the QALY calculation.

Q. Yes.

A. Yes. So it is not the QALY per se that captures the

financial --

Q. Well, it is a key input into the QALY.

A. It is a key input into the cost per QALY.

Q. Yes.

A. Yes.

Q. So subject to that caveat, you are happy?

A. Yes, yes.

Q. So that is the first point you make on economic value, we have been through the user benefits and the customer benefits, and we agree that the QALY captures those?

A. No, I did not say that, I said that the cost per QALY captures the customer benefit, and, as I have just pointed out, it does not capture, as given by 10.2, it may not capture all of the user benefit.

Q. Yes, but it is conservative, therefore. It captures the customer benefits.

A. Yes, okay, I will accept that.

Q. It may not necessarily capture other benefits to the patient.

A. Yes, I will accept that.

Q. So I think we agree.

A. I accept that, yes.

Q. So that is your first aspect of economic value. I now want to move on to your second aspect of economic value which is what you call normal competition.

Now, your basic point -- well, let us look at what you say in the report. It is at {XE3/3/4}. You see, Professor, paragraph 14, we saw this earlier, I just want to remind you in case you have forgotten. You say at the bottom, I quote:

"... a QALY analysis says nothing about what the price would be under normal competitive conditions."

Do you see that?

A. Yes.

Q. So for you, the key concept is normal competition; correct?

A. Yes.

Q. Now, I would suggest to you there are a number of abnormal features of pharmaceutical markets and I want to run through these with you to see if we agree or disagree. The patient who pays for the medicine or who consumes the medicine does not pay for it.

A. Prescription costs aside, yes.

Q. Subject to prescription costs, yes.

A. Yes.

Q. As we discussed, indeed, more often than not, the patient will not know or care what the medicine actually costs?

A. Mm-hm, yes.

Q. Now, because the patients do not pay the full cost at

the point of purchase, they are much less sensitive or insensitive to the drug's price. All they really care about is getting the best medicine they can lay their hands on.

A. Yes.

Q. Now, in a normal market, by contrast, a consumer would only, or certainly mainly, care about the price?

A. No, they would care about the benefit they are getting at that price.

Q. They would care about quality as well?

A. Or quantity as well.

Q. But price would be uppermost in their minds as well?

A. No, they would care about the marginal utility that they are getting from the commodity at that price: what is the benefit I am getting for the cost of paying the price?

Q. Well, I am talking about a non-pharmaceutical market.

A. Yes, so am I here. When you buy something, you want to know what the benefit is that you are getting from the product.

Q. I understand A-level economics.

A. Right. But you are only talking about the price, then.

Q. Well, I am asking you will they care about the price?

A. They will care, obviously.

Q. Of course they care.

A. Yes, but it is not the sole component of their caring.
Q. Fine. Now, the other abnormality is you cannot walk into a shop and choose a prescription medicine. The prescribing doctor makes that choice for you and gives you the prescription. Without the prescription you cannot get the product.
A. Certainly true.
Q. You depend on your doctor to represent your interests because you lack the knowledge as a non-doctor to make an informed choice yourself?
A. True.
Q. And because the government requires prescription medicines to be dispensed by a prescribing doctor?
A. True.
Q. Now, interjecting someone else's judgment into decisions, it disrupts the signals in terms of the consumer's own preferences, in terms of what the market should produce. To put it another way: consumer sovereignty over prescription medicines is limited.
A. True, I would agree.
Q. Now, another abnormality is that the ethically understood restrictions on the activities of a doctor are much more severe than, for example, a barber. The doctor's behaviour is supposed to be concerned with the patient's welfare which would, for example, not be

expected of a salesman?

A. True.

Q. Now, the prescriber who prescribes the medicine does not pay for it either, the prescribing doctor?

A. No, that is true, yes.

Q. Again, in many cases, the doctor will not know or frankly care about the cost of the medicine?

A. True.

Q. Another abnormality is we have a centralised monopoly buyer in the form of the NHS?

A. Yes, that is true. You have missed one agent out, of course: the pharmacist who probably does know the price and may be allowed to generically substitute for branded products.

Q. Yes, they may get a cut and they may --

A. Yes.

Q. Yes, that is fair.

A. Another abnormality, yes.

Q. Another abnormality, correct.

A. Yes.

Q. And there is a monopoly buyer which again is not normally the case.

A. Monopsony, yes.

Q. Now, not only do we have a monopoly buyer in a centralised public system, but that buyer is unusual

because in addition, the buyer has a suite of regulatory powers that it can deploy in the context of the system. So you mentioned the PPRS and the VPAS. Are you aware of the 2017 Health Service Medical Supplies (Costs) Act?

A. Not by heart, no.

Q. Well, let us have a quick look at that. It is at {XN8/9}.

A. Thank you.

Q. If we can go on to -- well, you can see, Professor, at the top of the page, if that can be made bigger, please, have a read of it, Professor, but essentially what this does is it was intended to plug what was perceived to be a gap in the legislation to allow the regulation of generic prices outside of the voluntary scheme. Does that ring a bell?

A. Yes, and this is 2017?

Q. Yes.

A. Yes.

Q. And you are also aware of Scheme M, I presume, Scheme M?

A. Yes.

Q. Let us have a quick look at that, it is at {XG/12/13}. You can see 28, the second part:

"... should the Department identify any significant events or trends in expenditure that indicate the normal market mechanisms have failed to protect the Department

from significant increases in expenditure, then the Department may intervene to ensure that the NHS pays a fair price for the medicine(s) concerned."

So there is the possibility of intervention under Scheme M., it no longer exists, but at least at the relevant time this was a possibility. Are you happy with that?

A. Yes. Well, that is what it says, yes.

Q. Yes. Now, again, in a normal market the customer cannot beat you over the head with a suite of regulatory price control levers, can they?

A. In a normal competitive market --

Q. Yes.

A. -- no.

Q. No. Now, a couple of final abnormalities. Entry into the market at the manufacturer level is controlled by the fact that you need a marketing authorisation which is typically preceded by years and years of clinical and safety trials?

A. Yes.

Q. By contrast in a commodity market you can enter tomorrow without any equivalent regime?

A. Yes.

Q. You also cannot increase the demand for a prescription medicine by advertising, can you?

PROFESSOR WATERSON: Just to point out that of course there are many markets in which there are regulations. You cannot enter as a restaurant, for example --

MR O'DONOGHUE: Yes, you need a licence. That is perfectly fair, Professor, that is extremely helpful.

A. Or to practise law, for example.

Q. Thank God for that.

Professor, I did not get your answer, but you agree that the restrictions on advertising of prescription medicines is a pretty severe restriction compared to a normal market?

A. Well, it is a restriction. There is lots of restrictions, as we pointed out. Whether it is more severe than any of the others, I do not know.

Q. In a normal market, I can try to increase the demand for my product by spending on advertising. I cannot do that for a prescription medicine.

A. True. Some people would argue that you could as a licensed person try to increase the demand for your services because the customer does not have any information over what the outcome is going to be other than relying on your knowledge, but, yes, whether it is more or less severe, it is certainly a restriction.

Q. Yes. Another abnormality is that the patent system places a numerical limit on the number and period for

which entry can occur?

A. Yes.

Q. A couple of final points. Because we have a centralised public health system, we do not have a market in which people can buy and sell risks to their health. There is no market for that. Correct?

A. True.

Q. Finally, the NHS's objective, contrary to a going concern, is not to maximise profit; its objective is to make people better and to use its budget as wisely as possible for these purposes.

A. Yes.

Q. I think we have identified about two dozen abnormalities, and I think there is no real disagreement between us. Now, do you therefore accept, in the light of these abnormalities, that the concept of normal competition needs to be applied in a modified way in a pharmaceutical market: it has to be applied with greater care and sensitivity?

A. Yes.

Q. But it must follow from that that when you criticise the QALY analysis because it does not address what price would be paid under normal competitive conditions, that is not exactly a fair criticism because, as you accepted, we are dealing in significant part with market

abnormalities?

A. Could we go back to my position paper or the paper where I state this with regards to the user, the consumer and the economic --

Q. Yes.

A. -- just to see what the context is.

Q. Yes, it is {XE3/3/4}. This is our third time, Professor, so is it paragraph 14?

A. Yes, 13(c) and 14, yes.

Q. Yes. You say at the bottom:

"... a QALY analysis is not informative for assessing economic value in that a QALY analysis says nothing about what the price would be under normal competitive conditions."

That is your criticism. The point I am putting to you, which you have accepted, is that in this case, or in pharmaceutical markets, we are dealing with a series of market abnormalities.

A. Mm-hm, yes, and so the cost per QALY analysis is not informative for assessing economic value under normal competitive conditions, yes.

Q. Yes, but your template is normal competition. The point I am putting to you is that in these markets there are abnormalities. So is it really a fair criticism to say: well, the template is normal competition, because you

have accepted there are abnormalities. Do we not have to modify the assessment of economic value because of these abnormalities? That is the point I am putting to you.

A. I am not sure what the point is that you are putting to me. Are you disagreeing with my statement there --

Q. Yes.

A. -- or are you saying that I should not -- so my statement merely says that we should not assess economic value through the QALY with regards to a price being encompassed within the costs per QALY statement under normal competitive conditions, and I agree these are not normal competitive conditions, that is for sure, yes, but whether that is an unfair criticism of my statement, I am not sure it is or not.

Q. Well, let me put it to you in very simple terms. You say for this to be effective, it has to be an assessment under normal competition.

A. For what to be effective?

Q. For the QALY to be effective.

A. A cost per QALY analysis to be effective?

Q. It has to correspond with normal competition?

A. No, I am not saying that; I am saying that a cost per QALY analysis is not informative for assessing economic value because it says nothing about what the price would

be under normal competition.

Q. That is the very point. The point I am putting to you is that is a straw man because you have agreed there are abnormalities in pharmaceutical markets that have to be taken into account.

A. So if you are telling me that we are both agreeing that the cost per QALY tells us nothing about price under competitive conditions, I do agree.

Q. I am not saying that emphatically.

A. Okay, that is what I am trying to clarify.

Q. I am not saying that emphatically; what I am saying is we have abnormalities in the market and therefore if your template is normal competitive conditions, that is unsuitable as a measure for these markets given the abnormalities.

A. I am not sure -- so maybe we could go through a proof by contradiction. I am not saying that a cost per QALY would tell you anything about price under monopoly conditions either.

Q. Again, I think we are going round in circles. The point I am putting is a very simple one: your template -- your main reason for rejecting the QALY is that it does not correspond to normal competitive conditions. The point I am putting to you: if that is the yardstick, it fails to take into account the two dozen abnormalities we have

discussed and you agree with and therefore is inappropriate and requires modification.

A. So all that I am merely saying here is that if you are thinking about economic value and economic value can somehow be generated by information from a perfectly competitive market, the cost per QALY does not do that. Whether that is because of the abnormalities or not is the next point. So I am simply saying that the cost per QALY does not tell you about economic value as economic value relates to competitive conditions.

THE PRESIDENT: Mr O'Donoghue, I think the position is this: what Professor McGuire is saying is that the cost per QALY analysis is not informative for assessing economic value in a competitive market, and that is all he is saying.

A. Full stop, yes.

THE PRESIDENT: What you are saying, and I think he is agreeing, is that there are other reasons for inferring that the price in this market is not workable competition or normal competitive market, and he is also agreeing with that, but I think that is as far as the agreement is going. I do not think he is saying that your factors in any way --

A. Contradict the --

THE PRESIDENT: -- affect his answer on the QALY.

A. Yes.

MR O'DONOGHUE: Sir, it may be a submission point. I have put the point as I see it.

THE PRESIDENT: Yes.

MR O'DONOGHUE: It may be a submission point.

Let me put the question another way, Professor, and then I will move on.

If, as you agree, there are certain abnormalities, you would agree that when we are considering value to the customer and the user, if we are to conduct a coherent analysis we must factor into account these abnormalities, otherwise the assessment is simply not fit for the job?

A. Sorry, could you repeat the question there because I am not sure if you are asking with respect to a cost per QALY as used as an instrument to tell us something about value or you are asking something else.

Q. Well, let us keep this very simple.

A. Right.

Q. We have a market where the patients do not pay for the medicine and frankly, do not care about its price. We have a market in which the ultimate customer, the NHS, is underwriting the entire system and is not in the business of making a profit, is simply trying to ensure the maximisation of limited resources as best it can.

The point I am putting to you is that the template or standard for assessing economic value in that context cannot possibly be normal competition, it has to be some modified version of competition to reflect these abnormalities.

A. If that is an economic question, I would say yes; if it is a legal question, as you have pointed out, I am not a lawyer.

Q. Okay, well, let us move on, then. I think we have taken this as far as we can go.

Now, I want to come on to Dr Skedgel's assumptions, and you have a number of particular criticisms of those. I want to deal with some, what I would call, headline points to begin with. The first is the concept of QALY is now many decades old, I think it dates as far back as the 1970s; is that correct?

A. The concept goes back to about the 1970s, yes. The use by NICE is obviously since 1999.

Q. QALYs and their closely equivalent measures, they are widely used in western countries as units of economic health?

A. More than western countries, yes.

Q. In particular, NICE's work on QALY has given intellectual leadership to a number of countries around the world?

A. Yes.
Q. Now, QALYs are simply a metric to quantify health benefits at a particular cost?
A. QALYs are a metric to quantify health benefits. Cost per QALY then brings the cost in, yes.
Q. By accounting for both longevity and quality of life, the QALYs can help guide health decisions, increase consistency and transparency. They are a key part of the public policy framework for the National Health Service.
A. Yes, I would agree with that, yes.
Q. Now, we have heard a lively debate on the threshold and where it comes from, and I assume therefore you agree that no single number could ever capture perfectly the complexity in preferences for health, but at the very least, a QALY threshold provides a useful point of departure in terms of thinking about how to allocate scarce resources?
A. Are we talking about the NICE threshold now?
Q. For example.
A. Yes, so the NICE threshold is different dependent on guidelines and HTAs.
Q. Yes, we will come to that.
A. And it is different for specialised medicines, yes.
Q. Yes, £100,000, yes?

A. So it is a guide to decision-making and that guide at the threshold level may be altered as we see different patient groups, yes.
Q. Well, let us keep this simple for now.
A. Okay.
Q. We have £100,000 threshold for the specialised drugs.
A. Yes.
Q. £20,000, as you indicated, and then 20 to 30 in other contexts. We have two or three identifiable benchmarks that have been applied for some time.
A. Reasonable enough, yes.
Q. Now, without a cost per QALY analysis or something equivalent, NICE's work would lack a clear benchmarking value for calibrating value-based pricing?
THE PRESIDENT: Well, Mr O'Donoghue, are you putting to the witness that there is some kind of correlation between these thresholds, whatever they may be, and price or value as an economist would understand them in a competitive market, or are you saying that the thresholds are tethered to what?
MR O'DONOGHUE: Well, sir, at this stage I am making a simpler point --
THE PRESIDENT: Right.
MR O'DONOGHUE: -- which is for 24 years we have had a couple of commonly understood thresholds which have

been used consistently by NICE as its benchmarks.

THE PRESIDENT: Well, yes, but we heard yesterday from Dr Skedgel that the £20,000 threshold, to take an example, is one that in absolute terms it is impossible for him to justify, and the sense I am getting from your questions is that there is some kind of objective correlation between, let us say, the £20,000 and something, and I think you probably need to articulate what you say that something is so that we can see what Professor McGuire says about it.

MR O'DONOGHUE: Well, sir, there is nothing loaded in my question. I am making a basic point that for 24 years now NICE has consistently applied these metrics. We will get on to the detail of the assumptions and particular thresholds, but I am again in the foothills of understanding --

A. Well, it is not, actually for 24 years. It started with £20,000 per QALY; the £100,000 actually came in much later as associated with trying to, in my mind, reconcile a budget to monopoly patent prices as they rise through time, so they were having difficulty encompassing oncology drugs in particular and set up a different drug fund for that. So the threshold started at £20,000, that basic threshold has stayed there. As I said yesterday, it is probably -- if you

pushed Sir Michael Rawlins into a dark room and threatened him with a hiding, he would probably say that is because it was the average earnings at the time, and unfortunately in this country median earnings have not risen very much since then, so we are still somewhere between £20,000 and £30,000, and you know, inflation has been very low, just to pick up on a point earlier, until very recently, so, you know, £20,000, I am not sure where it comes from, I am not sure if I agree with it, but it is the regulatory standard and as I said yesterday, it is an empirical question which they are trying to bottom-out now and the Department of Health has now moved to a £15,000 per QALY based on that empirical analysis at York.

Q. Again, I am putting a very simple point to you, which is the £20,000 threshold, for example, has been used for more than two decades by NICE.

A. Yes.

Q. To put it another way, from a patient perspective, the willingness-to-pay may well be infinite, whatever the ins and outs of NICE, at least they are applying some metric to trying to capture in some reasonable way a concept of willingness-to-pay and value for money?

A. So now you are mixing up the user and the customer and, you know, a patient's value would be infinite and I am

trying to distinguish between that end user value and the customer's value, and I completely agree with you that the customer, as defined by the purchaser, is the NHS, and the NHS uses £20,000, let us say, as the starting point for that threshold based on the opportunity cost of treatments which are incumbent within the NHS so that if it gets new treatments, it displaces the older ones with the more effective ones.

Q. Yes, so for better or for worse, NICE has used these thresholds in a pretty consistent fashion as part of its decision-making?

A. Certainly true.

Q. Okay, now, let us move on to the three assumptions which you challenge Dr Skedgel on. Can we start with proportionality.

Just to recap on what Dr Skedgel did: phenytoin is a third-line treatment. He was unable to find an RCT of phenytoin in a third-line setting. I do not think it is disputed that there is not really such a trial, and in particular, I think it is common ground, but tell me if you disagree, that in the case of older drugs there is no economic justification for doing an RCT for that kind of product.

Now, he did, however, identify a trial of phenytoin versus oxcarbazepine in a first-line setting and

a separate trial of oxcarbazepine against other comparators not including phenytoin in an adjunct or third-line setting, and he therefore extrapolated from these studies to come up with an efficacy figure for phenytoin in the third-line.

As you say I think at paragraph 18(a) of your report he used a network meta analysis to make an indirect comparison. Happy with that?

A. Yes.

Q. We will come to the detail of the assumptions in a second, but the upshot of Dr Skedgel's assumption is that phenytoin is an effective third-line drug for patients; that is his conclusion.

A. Do you mean cost effective or effective?

Q. Clinically effective.

A. Clinically effective?

Q. That is his 6.9%. Do you remember that?

A. Yes, yes.

Q. Now, just take a step back for a second, we will come on to the individual studies in a second, just to take a step back. Are you aware that in 2012 lamotrigine, carbamazepine were recommended as first-line treatment for children, young adults, for newly diagnosed focal seizures, these were the two first-line drugs of choice?

A. In NICE, yes.

Q. Yes.
A. Yes.
Q. Were you here for the medical evidence during this trial?
A. I was not -- I am afraid I was not at the medical evidence as presented over the past week.
Q. Can I quickly show you what Professor Sander for the CMA said about these two drugs and how they compared to phenytoin. If we go to {Day6LH1/159:} please. It starts at line 22. If you can read that, Professor, and then --
A. From 22?
Q. Yes, line 22.
A. Where it starts "Thank you"?
Q. Yes.
A. Sorry, what am I looking at, line 22 on the left-hand side page?
Q. Yes.
A. It says:
"Thank you. If we go to the right-hand side ..."
Q. Yes. (Pause)
A. Yes.
Q. So the bit, Professor, I would like you to focus on is at the end. So it says -- so this is the question being put to him by Mr Johnston:

"What we take from this is when comparing phenytoin to the first-line drug for focal seizures recommended in the NICE 2012 guidelines it performs pretty much the same in terms of effectiveness but is less well tolerated. Would you accept that?"

Then Professor Sander from the CMA says:

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

A. I am presuming the 1.03 is an odds ratio of some sort.

Q. Yes.

A. Right.

Q. So he accepted that at least in terms efficacy, phenytoin was comparable to the first two of the first-line treatments.

A. Yes.

Q. Again -- I do not need to turn this up, it is at page {Day6LH1/161:} we have the same point in relation to lamotrigine. Let us quickly look at that.

A. Could I just ask before you turn the page, is phenytoin, its efficacy being assessed as a first-line treatment here or a third-line?

Q. It was in first-line, in monotherapy.

A. First-line, okay, sorry, thanks.

Q. {Day6LH1/161:16}, you then see:

"If we then go to the right ..."

Mr Johnston says:

"... we see in terms of time to 12-month remission is that phenytoin is not extraordinarily, but it is notably more effective than lamotrigine. That is right, is it not? It is at 0.89?"

And Professor Sander says:

"Yes, I take that."

I am putting a basic point to you which is for the first two off-the-rack the CMA's medical expert accepted that at least in terms of efficacy there was a good degree of comparability between phenytoin and these drugs.

You will understand the reason I put this to you, which is on that basis, Dr Skedgel's ultimate conclusion that as a starting point phenytoin is an effective anti-seizure medicine is(?) entirely surprising, is it?

A. Well, this is in terms of first-line of course --

Q. Indeed.

A. -- is it not, so he is then making an assumption that the relative risks hold in third-line, and they would be a very different patient set.

Q. We will come to that now.

A. Okay. So it is maybe not surprising, but it is not substantiated, would be my point.

Q. We will come to that. I do not agree with that.

A. All right, thanks.

Q. Now in terms of Dr Skedgel's assumptions, you do not actually say -- we have been over the Cramer point, I think you were here for that -- you do not actually say that he has left out of account any important phenytoin study, do you?
A. No.
Q. I mean, essentially your criticism is of the process and the proportionality assumption itself?
A. Yes, which is what my instruction was, yes.
Q. But you agree that you cannot say that he has missed anything important?
A. No, no, I am not saying that, yes. I am not agreeing that he has or has not. I am not saying that part, yes.
Q. That is quite important.
A. Yes, absolutely.
Q. And as we established earlier, you have not come up with a different assumption?
A. It was not in my instructions, as I think I replied to your question earlier.
Q. Well, again, you have had a year, you have had a position paper.
A. And I had other things to do. Read the news -- oh I wish, I wish!
Q. Anyway, we can agree you have not come up with any alternative assumption; correct?

A. That is certainly true.
Q. Now, can we look at what Professor Walker says. This is on the extrapolation from first-line to third-line. If we go to {XE6/2/13}, please. If you could read paragraph 11, please. (Pause)
A. Yes.
Q. Are you aware this evidence was not challenged in cross-examination?
A. As I say, I was not here.
Q. You were not here, fair enough. You are not in a position based on your expertise to suggest it is wrong, are you?
A. Not at all, yes.
Q. Now, in terms of extrapolation from first line to third line or from one area to another area, are you aware that NICE itself frequently engages in similar extrapolation?
A. Yes, it does, yes, sometimes. Not frequently I would say, sometimes, yes.
Q. Let us see about that.
A. Okay, but you probably know the literature better than me, then.
Q. Well, let us have a look at the 2012 guidelines. Now, for my sins, I checked the number of references to extrapolation and I found 44 just in the 2012

guidelines. Does that surprise you?

A. Extrapolations from one line of therapy to --

Q. Well, I searched for the word "extrapolation" within the guidelines and I got 44 returns. I am going to show you some examples, but --

A. So extrapolation to my mind means different things. You could have extrapolation over time, you could have extrapolation as you are trying to use it.

Q. Let us look at some examples, then, fair enough.

A. Right, yes.

Q. It is {XD1/6/897}. Do you see in the second box, trade-offs, do you see the second part:

"There was no evidence for topiramate as adjunctive therapy, but there was some evidence extrapolated for monotherapy from JME which found it to be effective and the GDG thought it would also be effective as adjunctive therapy."

So there I would suggest is a very clear example of NICE itself in the 2012 guidelines extrapolating monotherapy to adjunctive therapy?

A. And was this for a guidance assessment or --

Q. Yes.

A. Presumably it is a guidance assessment.

Q. This is the guidelines, yes. You do not disagree with that, that is what it says?

A. No.

Q. Can we look at page {XD1/6/782} in the same document. You see under "Introduction", the second paragraph, the second half:

"'... In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children provided the dose is established'. As a result of this, and with the agreement of the GDG [or GG] we have combined the data for adults and children in the refractory focal seizures review."

So that is another example of an extrapolation from one cohort to another. Are you happy with that?

A. Yes.

MR O'DONOGHUE: Then the other reference is {XE/121/44}. (Pause).

Sir, I need to check that reference. It might be a good time for a break.

THE PRESIDENT: Very good. We will rise for ten minutes. Thank you very much.

(3.29 pm)

(A short break)

(3.47 pm

THE PRESIDENT: Mr O'Donoghue.

MR O'DONOGHUE: Thank you, sir. Can we go to {XG/121/214},

please.

So Professor, this is a supporting document in the context of the 2012 guidelines, and if we can blow up the middle, please, where it says "Informed". It says:

"Informed by the evidence from Kwan and Brodie, the GDG assumed that the cost-effectiveness of different AEDs used as a first-line monotherapy would hold true for their use as a second-line monotherapy."

So that is another example of extrapolation from one line to another line. Do you agree with that?

A. Yes.

Q. We have seen the evidence of Professor Walker, we have seen what NICE itself does in extrapolation from one line to another. Now, what Dr Skedgel has also done is he found the Chen study; are you aware of that?

A. Yes.

Q. That study showed, from a cohort of 2,000 patients, the declines from the first-line to the third-line in terms of efficacy across a range of anti-epilepsy drugs were around 40%, whereas Dr Skedgel, in terms of his assumption extrapolation from first-line to third-line, assumed an 88% decline.

So you would therefore agree that Dr Skedgel's assumption based on Chen is extremely conservative: it is over double the decline observed in the Chen study.

A. Slightly different assumptions. The Chen study was, as you say, a basket of goods and Dr Skedgel is using just one drug, but -- but Chen is looking at a change over I think it is first-line, second-line and third-line, which he uses to support his assumption.

Q. But what Dr Skedgel says is, well, he has made an extreme assumption against himself which is let us take 40% from Chen, I will accept a decline of more than double that, so he is assuming against himself in a way. Do you agree with that?

A. They are not exactly like for like comparisons, but in comparing against Chen's study he is making a more conservative assumption in that sense.

Q. Now, I would put to you that based on what we have seen from Professor Walker, the significant extrapolations made by NICE itself and Chen that Dr Skedgel's proportionality assumption at the very least is a reasonable one?

A. I could agree with that, but I would also suggest that if there was a submission to an HTA body rather than to the guidelines maybe in the scenario analysis which Dr Skedgel undertakes which is only on specific aspects of the existing model, should have been widened to test out precisely that assumption of proportionality.

Q. Well, we will come on to the PSA.

A. Okay, well, it is not the PSA, it is slightly different.
Q. We will come on to uncertainty which includes the PSA.
A. Right, okay, I was talking about scenario assessment, though, rather than PSA, yes.
Q. You certainly accept now that he has done a PSA?
A. In response to my first paper, yes, he did, yes.
Q. Yes.
A. And it came out with a value which said that it was not cost effective, phenytoin was not cost effective compared to pregabalin.
Q. Well, we will come on to that. I do not accept that.
A. Okay.
Q. So that is proportionality. Can we now move to equivalence, again, just remind ourselves what he did. The trials linking oxcarbazepine in the first-line and adjunct settings, they tested different average doses, so to match the average dosages between the two trials as closely as possible, Dr Skedgel excluded the maximum dosage which was 2,400mg and pooled the 600mg and 1,200mg into a single average of 900mg.

This pooled average dose of 900mg, he then assumed that was effectively equivalent to a dose of 1,028mg in his equivalence assumption.

Now, you make two criticisms of his equivalence assumption: first of all, you say -- so this is at 18(b)

of your report, it is at {XE3/3/6}. Do you see in 18(b)?

A. Yes.

Q. Do you see that?

A. Yes.

Q. You say, and I quote there is "little justification", that is your first point, and your second point is no sensitivity. We will come back to the sensitivity.

Let us focus for now on the question of justification.

Now, if we go to Mr Hawkins' evidence, it is at his second statement, {XC1/6.1/14}, paragraph 47, he says, second sentence:

"Justification for this is given within the guideline [over the page] documentation although there are advantages and disadvantages to either approach."

So what Mr Hawkins is saying, I would suggest, is there is no single right or wrong answer; there are pros and cons to pooling or non-pooling. Do you agree with that?

A. I would, and I would suggest that that is the reason why it ought to be tested under a scenario-type of approach.

Q. We will come to that. Hold that thought.

A. Okay.

Q. Now, the other point on the equivalence is the Barcs

study; are you familiar with that?

A. The Barcs?

Q. Barcs. B-A-R-C-S. Let us have a look at it. It is {XF3/1/1}.

A. Oh, okay, yes. I pronounce it differently, yes.

Q. You will see, Professor, in the top left where it says the median reduction in seizures. Do you see that?

A. Yes.

Q. So it says and I quote:

"The median reduction in seizure frequency was 26%, 40%, 50%, or 8% for patients receiving 600, 1200 or 2400mg ... or placebo, respectively..."

So they say the effectiveness of oxcarbazepine increased with dose, and on that basis is not Dr Skedgel's assumption at the very least reasonable, if not conservative?

A. So this is talking about seizure frequency and Dr Skedgel's model is on freedom from seizure, so it is not exactly comparable, but --

Q. We will come to that point. I do not accept that.

A. So is it reasonable or not? Well, if you are comparing the sizes of apples to the sizes of oranges and they are all the same size, I would say it is reasonable in that sense.

Q. Well, let us move on, which is the point I think we have

just made, the dichotomous outcome assumption.

So again just to tee up what Dr Skedgel did. The key clinical trial that he relies on in a first-line setting, the Bill study, expressed efficacy in terms of the proportion of patients experiencing complete seizure-freedom without capturing any benefits from incomplete seizure-freedom, so he applied the same approach in his model, so that is the dichotomous outcome assumption. Are you happy with that?

A. Yes.

Q. I want to put a number of points to you on this.

First of all, do you agree with NICE -- let us go to {XF3/54/565}. Do you see under question 8, do you see that?

A. Yes.

Q. You see where they say seizure-freedom is the most important?

A. Yes.

Q. Yes? You presumably agree with that?

A. Wholeheartedly, but, as I understand it, it is a very rare occurrence.

Q. Well, let us look at the medical evidence quickly. It is at {XF4/30/2}. This is a joint paper from Professors Walker and Sander who were the opposing medical experts, and you see on the left-hand column, the second

paragraph, do you see where it says "straw poll"?

A. See where it says what?

Q. "Straw poll"? It is the second paragraph halfway down:

"Indeed, a straw poll ..."

A. Yes.

Q. It says:

"... a straw poll of our patients with chronic epilepsy has certainly emphasised to us that for most patients ridding themselves of seizures is their primary aim and anything less is unsatisfactory."

And presumably you would agree with that?

Now, the final piece of medical evidence is on {Day6LH1/134:15}, please.

A. Is that medical evidence you have just shown me or just the preference for patients to have seizure-freedom?

Q. Well, you can read as well as I can, it is a joint paper from the two professors where they say a -- what they call a straw poll of their patients, that is what they told them. Well, let us look at what Professor Walker said in the box, {Day6LH1/134:15}, please.

Do you see where it starts:

"So, yes ..."

A. Yes.

Q. He says:

"... I cannot emphasise enough really the importance

of seizure-freedom. I mean, in terms of changes to quality of life, I think people think: well, you know, if it is a seizure once in a month, you know, how bad is that? I mean, for many people these just have completely devastating effects on their lives. They warned around just constantly terrified that they are going to have a seizure ... I see ... people who have been seizure-free for [two] years and suddenly have a seizure, suddenly they are afraid to go to the supermarket, they are afraid to go out in case they have a seizure, it just has such a big psychological impact upon them, and sometimes people again ... people are not very good at predicting what it will be like if something were to happen to them ... It is not until they have had the seizure that they suddenly realise, you know, what a devastating effect it has had on them psychologically and also socially in terms of being unable to drive."

We can all wholeheartedly agree with that?

A. Absolutely, yes.

Q. That is on complete seizure-freedom. Now, you do not actually say that Dr Skedgel's assumption biases his results in any particular direction, do you?

A. In terms of this assumption?

Q. Yes.

A. No.
Q. Can we also look at what NICE itself concluded. It is at {XD1/6/1247}. These are the forest plots from the 2022 guidelines, and you will see from the forest plots that the confidence intervals cross zero for some of the products, but at least on the basis of the point estimate relative to other comparators it would be difficult to claim that phenytoin is any less effective in terms of incomplete seizure-freedom than the other products listed here; do you agree with that?
A. They do not cross zero, it is crossing 1 being no difference to a placebo, I think, and I do agree that it would be very difficult, as I pointed out, I think, in my first paper, looking at the variance of the effect that was reported from the meta analysis which was helpfully done by Dr Skedgel that it is very difficult to come up with a clear winner, if you like, yes.
Q. But on that basis, do you at least agree that Dr Skedgel's assumption is a reasonable one?
A. Reasonable?
Q. Yes.
A. In the sense of reasonable in that there is no difference between placebo and phenytoin, or reasonable in what sense?
Q. Well, he --

A. Which assumption? The dichotomous one, or --
Q. The dichotomous one.
A. Ah, so he is taking a -- well, again, I did not actually make much of this in my report, but I would have thought that you would want to undertake a scenario analysis of that to -- given the uncertainty of choice here, that would be my position. It is a reasonable starting assumption. You would want to test it.
Q. But you agreed with me that there is no reason to think there would be bias in any particular direction.
A. Not from this, no.
Q. Okay, well, that is the assumptions. I want to move to a different topic. We will come back to the question of sensitivity and uncertainty. I want to move on to a different topic.

So one of the points, as we said at the outset you make is that you distinguish the TA process from the guidelines, and you talk about the impact on generic pricing in a guideline context. Do you remember that?
A. Yes.
Q. Your point, I think, in a nutshell is that in a guideline context, NICE does not set or even indicate the prices?
A. It does not do that neither HTA or guidance, so that is a commonality. The price is not set through the HTA

process and neither is it set through the guidelines process.

Q. But you do make a distinction between the TA and guideline process at least in terms of indirect impacts on pricing; correct?

A. Yes, yes.

Q. Now, can I suggest as a starting point that you have not fairly characterised Dr Skedgel's evidence on this point. Can we look, please, at Mr Hawkins' statement. It is at {XC1/6.1}.

A. On which particular point I have not characterised fairly?

Q. Let us hear what Mr Hawkins says and then it will become very clear --

A. Okay.

Q. -- what I am putting to you. So it is Hawkins 2, page 5. So it is at paragraph 17. You see where he says:

"In principle, whilst there are some differences in methodology for considering cost effectiveness between the guidelines and TA methods ... I agree [that] these should not make a difference in this particular case."

So what Mr Hawkins is saying there is that the basic methodology and cost effectiveness is sufficiently similar for present purposes between the TA and the

guidelines; do you see that?

A. Yes.

Q. If we go to what Dr Skedgel has done, it is at {XE3/1/10}, paragraph 41, we have seen this, I think, more than once today, so he says in the second line:

"... I use, to the extent practicable, the approach that would be taken by NICE, had it been conducting an appraisal of phenytoin in a technology assessment or as part of a clinical guideline development ..."

So the point Dr Skedgel is making is that he is not stuck in a TA or guideline pigeon-hole when it comes to his cost-effectiveness methodology; he is applying an essentially common methodology to work out on the basis of his model whether phenytoin is good value for money.

A. Is that a statement or are you asking me something?

Q. Well, let me put this in a pointed question to you. You criticise Dr Skedgel on the basis that you say from a process point of view there is a big distinction between the TA process and the guideline process. What Mr Hawkins and Dr Skedgel are saying, I would suggest to you, is that in terms of the cost effectiveness assessment, the methodology between TAs and guidelines is a common one.

A. The methodology that is applied, yes. I would go a bit further and say that although I recognise -- and again,

I am not criticising the intrinsic quality of the model Dr Skedgel had put forward, and I am not saying that to the extent practicable it is not reflecting his time constraints or data constraints, but I would say that most of my criticisms on the assumptions stem from the fact that he did not undertake scenario analysis to deal with uncertainty in terms of the structure of the model, his scenario analysis as it was performed to my mind.

Q. We will come to that, but let us stick to this topic.

A. Yes.

Q. Again, I would put it to you that your criticism of Dr Skedgel in terms of this TA and guideline distinction is not a fair one. All he is doing in terms of cost effectiveness is applying a methodology that is common to TAs and guidelines. What he is saying is applying that common methodology phenytoin at the challenged 2012 prices is within threshold and, therefore, is good value for money, and that conclusion does not depend on any particular pigeon-hole.

A. I disagree --

Q. Do you agree with that?

A. I disagree with that.

Q. Why?

A. Well, partly because of the conclusions that are reached in the sense that, as James Hawkins has said, generally

speaking, guidelines apply a £20,000 per QALY threshold, and the HTA threshold would be a range depending on the patient body going from £20,000 to £30,000.

Q. On his model he is below £20,000.

A. Pardon?

Q. On his model he is below £20,000.

A. Yes, but the uncertainty, the probability sensitivity --

Q. We are going to come to uncertainty.

A. Okay, but that is an important distinction because his --

Q. Well, let us stick to the methodology.

A. All right.

Q. Do you agree --

A. I am sticking to the methodology in the sense that the threshold is £20,000 for guidelines and £20,000 to £30,000 and beyond for HTA.

Q. And that is the threshold he has applied.

A. He has applied £20,000 to £30,000 within trying to present his PSA results --

Q. His base case results, all of them, are below £20,000?

A. Pardon?

Q. His base case results, all of them, are below £20,000?

A. His deterministic result --

Q. Are all below £20,000.

A. He only has one, and it is below £20,000, but when he

applies probability sensitivity analysis, there is a 50% chance that it goes up to and beyond £30,000.

Q. We will come to the uncertainty. Let us stick with the methodology. In terms of his cost effectiveness methodology, he has applied a common methodology to the guidelines and the TA process.

A. Part of the methodology to my mind is the threshold against which you are comparing, and in the guidance, as James Hawkins pointed out, the guidelines uses £20,000, above and below, and HTA uses a range, and part of that range is £20,000 to £30,000.

Q. I would suggest to you it is actually quite simple: Dr Skedgel has used a common cost effectiveness methodology used by NICE in a TA and guideline context, and he has, through his model, concluded that the phenytoin prices in 2012 are below £20,000 and, therefore, good value for money. That is the long and the short of what he has done.

A. Yes, I disagree with that. As I say, I do not think it is robust and I do not think it is necessarily reliable given that he has not tested out his assumptions in a scenario way which you might expect under an HTA.

Q. Well, let us move on. We disagree about that.

Now, you at least agree that the guideline, the NICE guidelines, expressly refer to QALY measures?

A. Yes.
Q. There is at least, I would suggest, a reasonable expectation that the NICE guidelines will be followed, including to use medicines that are good value for money?
A. The NICE guidelines are recommendations essentially to clinical practice, and if there is good reason or not, and whether they are or not, there may be exceptions, so I do not know how widely they are applied in practice with regards to clinical practice, but individual clinicians using them, but they are giving you a standard of care.
Q. Well, let us look at what Rawlins says about this. It is at {XF3/27/1}. You see the first paragraph. Professor Rawlins is a critical person within NICE; correct?
A. He was the first President of NICE. He has now moved I think to -- did he not move to Pfizer or one of the drug companies after he left NICE, I can't remember.
Q. You may well be right, but at least in this context he is wearing a NICE hat, you see that --
A. Whether he is critical or not is what I was issuing about.
Q. Anyway, so what he says here is:
"Where NICE reaches a positive conclusion about the

use of a particular health technology ... there is a legal requirement for the service to make it available ..."

So that is the funding point.

Then he goes on to say:

"Although this legal obligation does not apply to technologies recommended in ... guidelines, there is ... a reasonable expectation by the [CQC] for NHS healthcare professionals to use NICE's clinical guidelines as the basis, where appropriate, for their clinical practice."

So that is the point I am putting to you.

A. I think they are used as a benchmark by the CQC, yes.

Q. Indeed, yes.

A. Yes, okay.

Q. And professionals?

A. I cannot comment on that, I do not know about clinical practice that much in terms of its variance.

Q. Let us look at what the guidelines say. It is {XF3/29/2}, please. The first paragraph.

This is the introduction to the guidelines which says:

"Your responsibility.

"The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgment,

professionals and practitioners are expected to take this [guidance] fully into account, alongside the individual needs, preferences and values of their patients or the people using their service."

So a recommendation adopted in a guideline, NICE's expectation is that it would be followed in practice?

A. Yes, you could read on and read the first sentence of the second paragraph if you wish.

Q. Please do.

A. "Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it."

Q. Yes. Now, would you agree, therefore, that the NICE guidance would at least affect the uptake of generic medicines in the UK?

A. Yes, it could do, yes.

Q. I would suggest it is more than that: where a generic is recommended that will affect its uptake. It is an endorsement.

A. It is a recommendation, not a statutory obligation. So it should affect it, yes.

Q. Yes, well, let us have a look at what the study says on this. It is at {XF3/52/3}, please. Can we go to the first page just to show the Professor what we are

looking at {XF3/52/1}. The title is:

"Does NICE influence the adoption and uptake of generics in the UK?"

Do you see that?

A. Yes.

Q. If we then go to page {XF3/52/3}, please, you see in the bottom left in the final paragraph?

A. Where it says "Incumbent firms ..."

Q. "TAs ..."

A. Pardon?

Q. "TAs..."

It is the second sentence, Professor.

A. The second sentence of the last paragraph --

Q. So it starts:

"TAs have ..."

THE PRESIDENT: He is looking at the left-hand column, not the right-hand column, Professor.

A. I am looking at the right-hand column, but --

THE PRESIDENT: Yes, I think that is wrong.

A. Okay, so "The underlying" -- is that the sentence?

THE PRESIDENT: I think it is left-hand column, the big paragraph from the bottom up beginning:

"TAs have the capacity ..."

Have I got that right, Mr O'Donoghue?

MR O'DONOGHUE: Thank you, yes.

THE PRESIDENT: Do you see that, Professor?

A. Yes, so what am I specifically --

MR O'DONOGHUE: Let me read out the quotation, the second sentence.

A. "The underlying hypothesis..."

Q. Yes:

"... generic uptake may be more attractive if guidance states that the molecule is recommended for the treatment of certain condition, as this is an indicator of the superiority of the molecule with respect to other competing molecules. NICE may also recommend the cheapest version of a sample of similar medicines (with different active ingredients) ... thus have a positive impact on generic usage."

So they are making a rather obvious point, I would suggest, which is if a generic has been recommended as being good value for money by NICE, that is something of practical significance to the market.

A. I do not think I disagree with that, and it does not amend my earlier statement. It says "may be more attractive".

Q. You would also presumably agree that all else equal it would be harder to sell a drug that was not recommended by NICE as a generic?

A. That is certainly true.

Q. We see this in the context of AEDs. Were you aware, for example, that there are about 30 AEDs on the market and only 18 have been recommended by NICE?
A. There are 30 on the market, but only 18 -- I had not been made aware that only 18 had been recommended. I knew there were more than 20 on the market, yes.
Q. Yes, well, let us have a quick look at that. It is at {XF3/54/29}, please. Do you see the top of the page?
A. Yes.
Q. "There are currently more than 30 ... (ASMs) ... 18 ... recommended ..."
A. Right.
Q. Happy with that?
A. Yes.
Q. Now including of course phenytoin --
A. This is from the 2020 guidelines or the 2012? I presume the 2020.
Q. I think this is the cenobamate submission.
A. It is the what?
Q. The cenobamate appraisal.
A. Okay, right.
Q. So I think you are right, Professor, it is around 2020.
A. So it is after 2020.
Q. Around, around that period.
A. No, it is after 2020, yes.

Q. Yes. So on this basis, as a recommended ASM, phenytoin is in relatively selective company. Do you agree with that?
A. If by that you mean that it is one of the 18 recommended, yes.
Q. And it is not one of the 12 not recommended?
A. I have no -- of course, yes, that is true, yes.
Q. Now, given, as I think you agree, a positive NICE recommendation is useful, if not important --
A. Useful I would say, yes.
Q. Yes -- is not this another reason why a manufacturer, at least a sensible manufacturer, would wish its prices, where possible, to be at least consistent with the NICE thresholds for value for money? To put it another way, there would be a real risk in trying to sell a medicine that fell outside or plainly outside the NICE thresholds.
A. I think, to put it another way, if the medicine went above the recommended threshold --
Q. You would have a problem.
A. -- it would not be recommended.
Q. Yes.
A. Yes, that is certainly true.
Q. And you may have problems selling it?
A. Yes, and if there was any uncertainty around whether it

was above or below the threshold, it may not be recommended on the basis of cost effectiveness alone.

Q. Now, it is clear when NICE is considering the value of a drug it takes into account the price of that drug as a cost input in the cost effectiveness model?

A. Yes.

Q. And NICE will for these purposes try and obtain the most accurate real world data it can on the prices in question?

A. Yes, although it stuck -- well, again, are we talking about the HTA process or the guidelines process, just to --

Q. Both.

A. Both, well, for the HTA process it gets the list price, and it may or may not have access to negotiated prices past the list price.

Q. And it would have the drug tariff?

A. Pardon?

Q. It would have the drug tariff?

A. It would have the drug tariffs which will have the list price, yes, for the HTA process.

Q. And it may be aware of discounts, as you say?

A. Yes.

Q. Now, it is also clear, I would suggest, that NICE can and does indicate that at a particular price point

something is not good value for money and it may indicate the level of price reduction that would be needed to achieve good value for money?

A. Under the HTA process, that is true, and they may enter negotiations with any individual company who has a patented drug to negotiate prices down. For a guidelines process where you are dealing with the generics and they go into the guidelines rather than an HTA process, I would say, that would not occur because the generic price would already have been established by potential or actual competition.

Q. Well, let us look at that, I do not accept that.

A. Okay.

Q. Now you raised yesterday the example of levetiracetam; do you remember that?

A. Yes.

Q. So let us have a look at what NICE said about that in 2012. It is {XF3/29/29}. Do you remember this?

A. Yes.

Q. About a third of the way down:

"Levetiracetam is not cost effective at June 2011 unit costs ... It may be offered provided the acquisition cost of levetiracetam falls to at least 50% of [the] June 2011 value documented in the ... Drug Tariff ..."

So I would suggest to you this is about as clear a signal as you can imagine from NICE that if the producer of levetiracetam wishes to be in the ballpark of being considered good value for money they have to make at least a 50% reduction in price to be considered cost effective.

Do you agree or disagree with that?

A. I disagree. I disagree in two ways. One, it says it may be offered, so it is a conditional statement, it may be a signal, that is true, if that is what you are saying, but also I was not there, and I think there is at least two interpretations, and, as I said yesterday, levetiracetam was going off, the clinicians knew it was going off-patent in 2011 and so they are trying to future-proof their guidelines, I think -- that is my interpretation, I was not there -- they are trying to future-proof their guidelines recognising that once a drug comes off-patent in the first year, it usually falls by 50% to 70%.

So I think they are saying: we expect the price to fall by -- again, my interpretation, and happy to have your interpretation as well, but my interpretation is that it is an expectation that the price will fall and in fact it did, as I said yesterday, from £28 per 250mg to £1 per the equivalent dosage, £1 something, I forget

the --

Q. Let me just put two points to you.

First of all, they are saying at the 2011 prices they would not recommend it.

A. True.

Q. They are also saying that if it got to the level of 50% or below, it is then in the ballpark.

A. It may be offered, yes, it may, may, yes.

Q. So both of those on any view are price signals.

A. Well, you see, that is where we disagree on interpretation. I think it is a signal, but it is also an expectation in that I think the guidelines committee knew it was going to be a generic afterwards, and it would -- you would say this is a signal that it should drop the price 50%, I say that they are expecting the price to be dropped by at least 50%.

Q. Well, I can see if it reduces by 70% that is even better value for money.

A. So that is why I say at least.

Q. I would suggest to you at a minimum what they are saying here is that at a reduction of 50% it is in the ballpark of being good value for money. There is no other logical reason they would indicate the 50% reduction level, is there?

A. It says "at least 50%", and that I think is in the

ballpark, to use your phrase, of what we would expect to happen if a drug comes off-patent as it was doing in 2011.

THE PRESIDENT: Mr O'Donoghue, how are you doing for time?

MR O'DONOGHUE: I think I am okay, sir, if we are finishing at 5.00.

THE PRESIDENT: Well, I think five-to would be better than 5.00.

MR O'DONOGHUE: Yes, well I will do my very best.

Now, Professor, if we go to your report, it is at {XE3/3/15}, you say there at the top:

"The highest product price required to remain within the NICE threshold could be '[backward]-engineered" through backward induction, although this is not meant to be how the NICE guidance should be applied."

So you were clearly saying there that from the published prices and NICE thresholds you can backward-engineer a price at which you would be in the ballpark of cost effectiveness under NICE thresholds?

A. Yes, and, as I said yesterday, I think possibly unfortunately that is going to increasingly happen as VPAS is aligned with NICE thresholds, as is expected by the Department of Health, NICE in a number of publications they have put out, because that will mean the manufacturer of a patent will get all of the

producer surplus.

Q. Let us put this in basic practical terms: I as a manufacturer may have a price that I backward-engineer, works out at a QALY of -- an ICER of £35,000. I know based on the thresholds I have no realistic prospect of that being recommended at that level of price, and if I am being rational, to be in with a chance of being recommended with the benefits that come with that, I will backward-engineer my price to be at or below the threshold. That is what any rational manufacturer would do, surely?

A. As the President pointed out yesterday, it might be kind of difficult to do this except with educated guesswork because you do not know the comparator that NICE might use, you do not know the precise calculation that NICE might do, but, yes.

Q. Well, you are the one saying here it could be backward-engineered.

A. It could be, but it would be imprecise at best, but I guess good guess at best.

Q. Well, it would be useful, I would suggest.

A. Certainly.

Q. Now, I am going to move on finally to the various points around uncertainty which you have mentioned.

Now, your primary criticism in your report was the

lack of a sensitivity analysis, and I think I counted 27 references to "sensitivity" in your first report, and you at least now accept that Dr Skedgel in response to that has done a PSA and that a PSA is a widely used technique by NICE in its assessments.

A. If you are asking do I agree with that, I would say that -- two things -- one is Dr Skedgel did very helpfully do that in his second submission, I think, to undertake a PSA analysis which is around parameters, and that showed that there was a 50/50 chance that given the sampling uncertainty that phenytoin as compared to pregabalin would meet a threshold of £20,000 per QALY, which would be consistent with the guidelines.

Secondly, the second point would be that although Dr Skedgel refers to the second form of uncertainty that NICE would probably insist upon, given lack of evidence, the scenario analysis which is about the structure of the model and he talks about doing a scenario analysis, again, I would say that is mainly around parameters rather than the actual structure of the model itself.

Q. Sorry to stop you there. That is not a point you mention in your report, that is a point you mention in your position paper for the first time; is that correct?

A. I think -- I stand corrected if you say I am wrong, but I think I said it in the second submission that they

should have -- they might have, to improve the quality of his report, moved to a scenario analysis, but certainly there are two types of analysis and he has done a very good job on the first one.

Q. You knew when you put in your position paper that at that stage it is very difficult for Dr Skedgel to do anything further. It was rather late in the day to raise this, was it not?

A. I think it was very difficult for Dr Skedgel to do the whole modeling process, he had a very tight time constraint.

Q. Indeed, and he deserves credit?

A. Absolutely, yes.

Q. Now, we can all agree that if each and every input in the model passed the 95% confidence interval that would be ideal, but we know in the real world of health economics that uncertainty is pervasive?

A. Yes.

Q. Now, we have seen -- I put this to you a number of examples -- that one of the ways NICE deals with uncertainty is they extrapolate from one line to another or from one cohort to a different cohort. So that is one of the ways you contend with uncertainty.

A. Yes, I think they have got stricter over that, and they would ask for more scenario analysis, but, yes, they do

that, yes.

Q. Well, they did that in 2012, we saw that.

A. Yes, but they have got stricter, is what I am saying in terms of the methods.

Q. Now, Professor Claxton who I presume you know well --

A. Yes.

Q. -- he is one of the world's leading experts in health economics and has served as a member of a NICE appraisal committee since 1999, and he has written what I think is known as the White Book in the sphere of health --

A. Blue Book, blue.

Q. Well, I have got them both.

A. Yes, it is the blue one in your right hand.

Q. This is --

A. That is the left hand and that is the white one which is --

Q. Which is Professor Claxton --

A. -- not as big in terms of revenue for him as the Blue Book.

Q. Let us have a look at the White Book, it is at {XF3/69}, please.

If we can go two pages on, please {XF3/69/3}, this is The Irrelevance of Inference. We can blow up the abstract. He said:

"The literature which considers the statistical

properties of cost-effectiveness analysis has focused on estimating the sampling distribution of either an [ICER] or incremental net benefit for classical inference. However it is argued here that the rules of inference are arbitrary and entirely irrelevant to the decisions which clinical and economic evaluations claim to inform. Decisions should be based only on the mean net benefits irrespective of whether differences are statistical significant or fall outside a Bayesian range of equivalence. Failure to make decisions in this way by accepting the arbitrary rules of inference will impose opportunity costs which can be measured in terms of resources or health benefits forgone."

So what Professor Claxton is saying is that the rigid adherence to the normal rules in an RCT context of 95% confidence intervals, that is an inappropriate approach when it comes to decision-making in health economics.

Do you agree with that?

A. In this rather old paper that is what he is saying, yes.

THE PRESIDENT: So you do or do not agree?

A. I agree that that is the argument in this paper, yes, but -- well, if you want me to elaborate --

MR O'DONOGHUE: Are you saying it is wrong then or wrong now or wrong both?

A. I am saying that that is still consistent with undertaking a probability -- his argument here, which says basically if you are making decisions you ought to make decisions on a range of the states of the world that are outcome states, is one way of characterising uncertainty, but that is still consistent, as he puts in that Blue Book and the White Book, that you should -- with a position that he upholds as well -- that you should undertake probability sensitivity analysis.

Q. Which Dr Skedgel has done.

A. Yes, he has, yes, and shows that there is big uncertainty around the mean values.

Q. Let us come to it, I do not accept that, let us come to that. Now can we look at what NICE itself says at {XF3/70/4}. At the bottom of the page they say:

"When developing guidance ... NICE bases its decisions on the best available evidence. This evidence is not always of good quality and is hardly ever complete. Those developing NICE ... guidance are therefore inevitably required to make judgments."

You presumably agree with that?

A. Yes.

Q. Now you yourself have written about uncertainty in a book that you edited which I also have.

A. I hope you bought it.

Q. I did. It is the first -- you remember this book?
A. Yes, yes.
Q. You edited the book and you wrote the first chapter, I think.
A. Yes.
Q. So if we can look at your conclusion in chapter 1, it is at {XF3/72/2}. It is in the middle where you say "Indeed". You say:

"Indeed there are few occasions when even a rudimentary back-of-the-envelope calculation of critical costs and effects will not serve to guide decisions. Economic evaluation remains a useful tool that focuses attention on the necessary choices relating to the allocation of resources and is capable of application in various degrees of sophistication."

So on your view, a search for perfectionism or perfect confidence intervals at every juncture in health economics would not be appropriate?
A. No, I do not think that follows. I am saying that even a rudimentary approach would provide you with some information. Obviously, the better the approach and the better the data then the better the decision that arises from that.
Q. We can at least agree that what Dr Skedgel has done is a bit better than the back of an envelope?

A. Yes, but, as I have pointed out in my papers and position paper, whether it aligns with NICE's methodology -- and in fact Dr Skedgel in his own report says it does not, but he has done the best that he can given his constraints, and I would agree with that.

Q. I want to turn finally -- and I want to take this quickly -- to the points you make around the structure of the model and sensitivity uncertainty.

We pick this up in your position paper because that is the first time you have mentioned, I think, most of these points, which I would suggest to you is not fair to Dr Skedgel, but I will put these to you in any event.

So if we can go to {XE6/6/16}, please, it starts at page 16. You have a handful of points that I want to run through quickly. The first point you make at paragraph 50, you say that Dr Skedgel does not conduct appropriate scenario analysis.

Now, you do not give any indication in this position paper what you consider would have been an appropriate scenario analysis.

A. I think it is implied by saying "of his structural assumptions", and the structural assumptions are the ones which we have discussed earlier about proportionality, equivalence and dichotomous. Dichotomous maybe not, because -- well, it might do,

I mean, again, it gets back to the discussion of what James Hawkins was saying about a three-state versus two-state model, etc, and then the assumption of what I was getting at, the structural assumptions, and, as I think I emphasised in the position paper, was the proportionality and equivalence assumptions.

Q. Well, I would suggest to you that Dr Skedgel has done something actually quite dramatic, which is he has more than halved the efficacy percentage he arrived at applying the three assumptions that we have been through.

A. Half from what?

Q. From 6.85% to 2.9% efficacy.

A. Okay. You see, I would say that was more of a -- I mean, it is splitting hairs here a little bit, I think here, but I would say that is more of a probability sensitivity analysis where you take one of the parameters and change them. What I would like to see is a change in the proportionality assumption and a range of values going forward to see how it affects the model. In the event, it probably -- well, anyway, yes.

Q. Well, he has more than halved his efficacy estimate, and even taking that large haircut, he is still within the £20,000 to £30,000 threshold.

A. Yes.

Q. You heard the evidence today put to Dr Skedgel that both of the medical experts agree in a third-line setting that the efficacy is around --

A. Ballpark, yes.

Q. -- 5%, ballpark. Now, on that basis, his base case of 6.85% is in the ballpark.

A. Yes, yes. I would still want to see it addressed more formally, I suppose, would be my position.

Q. Well, he has undertaken a dramatic haircut, and he is still within threshold.

A. Mm-hmm.

Q. Now, his 2.9% haircut is equivalent to a 95% reduction in efficacy between first line and third line, whereas his proportionality assumption, in the base case, was an 88% reduction. So, again, on proportionality he has applied a significant sensitivity to his analysis to keep him within threshold.

A. On the proportionality assumption?

Q. Yes.

A. By dropping the efficacy down to that level?

Q. Yes.

A. So what I would like to see, and maybe I have not explained it well enough, there is -- and what I think the structural uncertainty that NICE would like to see -- I am not saying they always get this -- would be

to say: well, how does that affect your underlying model and then, within that underlying structural change, show us the probability sensitivity analysis on top of that.

Q. Why have you not done that if it is so wonderful?

A. Because, as I have said, it was not in my instructions. My instructions were to see whether the model that was produced by Dr Skedgel was in line with the NICE methods.

Q. So you are content to throw rocks and not give an alternative?

THE PRESIDENT: Mr O'Donoghue, we have had that question before.

A. And I think I answered it before.

MR O'DONOGHUE: Now the next point you make is at 51 {XE6/6/16}, if you read that paragraph. (Pause)

I am sure it is just me, but --

A. What am I looking at now?

Q. Paragraph 51, Professor.

A. Oh right.

Q. It may be my fault, but I read this as saying Dr Skedgel did not conduct a PSA in his first report and then the fact that he did it in his second report does not change his original conclusion or your original conclusion that his results are not robust.

Are you saying anything more than that?

A. Am I saying more than that these conclusions --
Q. That he did not do a PSA, now he has done one, and you are still not content; is that all you are saying there?
A. Yes, because, as we have heard earlier today, the range of sample uncertainty aids the decision-maker and when Dr Skedgel does undertake a PSA, he finds that the mean value around that sensitivity analysis is that phenytoin is not cost effective relative to pregabalin and there is a huge range of uncertainty in that mean expected value of the ICER.
Q. Now, the next point you make is at 52 {XE6/6/17}. You say, and I quote:

" ... Dr Skedgel appears to suggest that information from a PSA on uncertainty is somewhat inconsequential."

Where does Dr Skedgel say that?
A. So at some point -- and I would have to re-read the documents in the submission around the PSA -- he says something about how although his net monetary benefit value is negative, it is close enough to his deterministic value as not to change his opinion. I would argue that it should have changed his opinion because it does show that it is now flipped from being cost effective relative to pregabalin to being a position where at least centred around the sensitivity analysis it no longer is.

Q. So as you say Dr Skedgel says the upshot of his analysis is that the expected values derived from the probabilistic results are consistent with his original deterministic results?

A. Yes, that is what -- where is that? That is not on the page that I am looking at, but that is at the end of his conclusions.

Q. I think that is what you just said.

A. Yes. That is as I recall it.

Q. Now, if we go to Briggs, the White Book, {XF3/71/2}, please.

If you can look at page 194, if you look at the summary at the bottom of the page and then over the page, please. (Pause)

I think, Professor, what they are saying here is there are two separate but related decisions, one whether to adopt a recommended technology and two, whether to invest in research that could reduce uncertainty in the future, and then they state, and I quote:

"The first type of decision (in the absence of serious concerns of reversibility) should be made on the basis of expected values in order to minimise opportunity costs."

Now, I would suggest to you that Dr Skedgel's

analysis, and especially his PSA, shows that all comparators are similar with respect to costs and outcomes, and, therefore, it would be hard to argue that there is much possibility of phenytoin being substantially worse than pregabalin.

So Dr Skedgel's approach, I would suggest, is at least a reasonable one and indeed on the basis of the White Book is in fact the recommended one.

A. Do I agree with that or --

Q. Yes.

A. No, I disagree, and I disagree on two levels: one is on the modelling that Dr Skedgel has undertaken and what you have just said, that there is no difference between the costs and the outcomes, he shows that there is. There is a dominance in cost effectiveness across a range of the other -- a range of the other medicines according to his modelling, so I think that is a wrong statement.

The second reason I disagree is that this is -- so this summary, this conclusion, is based on something called the expected value of perfect information which is taken from financial economics and imposed on health economics about decision-making, and it is a completely different way of looking at uncertainty, it says basically you should look at the uncertainty associated

not only with the inputs to any decision but also the outcomes that flow from that decision, so the outcomes are part and parcel of that uncertainty calculation, whereas with PSA and scenario analysis, you are just looking at the impact that differential inputs have on the outcomes.

NICE actually looked at expected value of perfect information in a taskforce in 2020, and their conclusion was they did not see how it could be used at this point in time within NICE assessments.

Q. Well, let us go back to your position paper at 53 {XE6/6/18}. You see in paragraph 53 in the fourth line you say the deterministic and probabilistic assessments are, and I quote "close". Now, we have already seen in Claxton's paper The Irrelevance of Inference where he suggests that conventional statistical inference levels of 95% confidence are not the correct approach and that a 50 plus 1% is a perfectly acceptable basis for decision-making?

A. Do I agree or disagree?

Q. Yes.

A. That is what he says, but to elaborate on that, my instruction was: does the modelling that is undertaken by Dr Skedgel uphold the standards of the methodology which would be adopted by NICE. The Claxton 1997 paper

which you showed me and the Andy Briggs chapter which you showed me is about -- is talking about expected perfect value of -- the value of -- expected value of perfect information, and in 2020, the NICE taskforce said they did not see how that could affect their methodologies, so it is outside of my remit of criticisms because I am only really looking at whether Dr Skedgel's methodological approach was consistent with the NICE methodology as it stands and as it will do for the foreseeable future given that they have ruled out expected value of perfect information as an approach to dealing with uncertainty.

Q. But we have seen extensively in the 2012 guidelines in 2022 that even in the complete absence of any clinical evidence, never mind clinical evidence passing statistical inference levels of power, NICE was perfectly content to make a decision to recommend an AED in that context, and the standards you are putting forward for Dr Skedgel are utterly disconnected from the real world, I would suggest to you.

A. No, I do not think so, because if you take the 2020 guidelines that you have just referred to, they also found that it was a negative net monetary benefit, but they said that within that guidance, having seen that the cost effectiveness was not upheld, they still

said: let us go ahead with phenytoin, and --

Q. That is my very point.

A. But they did that not on cost effectiveness grounds, is my point, they did it on a wider set of criteria primarily led by the clinicians.

Q. Indeed, because they want to make a decision.

A. But not on cost effectiveness grounds.

Q. Well, they essentially binned cost effectiveness?

A. They essentially did, yes. You are not saying of course that we should bin Dr Skedgel's --

Q. No, I am not saying that.

Now, one final point, I see the time, at paragraph 54 {XE6/6/18}, you say, I quote:

"... NICE 2022 guideline is based on a wider set of comparators and places ... phenytoin within a wider sequential treatment pathway, while the Skedgel submissions only consider part of the pathway, third-line comparators alone."

Now, we know and we have known for many years that phenytoin is only used in a third-line setting, so it was therefore entirely appropriate for Dr Skedgel to consider his model in the context of the third line alone.

To put it another way, you are not seriously suggesting that he should have compared phenytoin

against other first or second-line AEDs, are you?

A. No, I am not, but where you use it and how you use it in therapy affects the population at risk, and I think the NICE guidance gives a better overview of that transition from first to second to third-line than just taking the third-line out as an abstraction.

Now, that may be a moot point, it might still be the same at-risk population that you end up with, I do not know.

Q. But we are only looking at third-line patients?

A. And NICE was saying: okay, let us look at treatment failure in the whole to see how we get to that population at risk by the time there are third-line therapies coming into play.

Q. When it came to phenytoin, they only compared it to other third-line drugs. That is the point?

A. So I am saying that the NICE guidance and cost effectiveness is more comprehensive in a sense than just taking the abstraction.

Q. My point is: well, so what, we are only interested in third-line?

A. Different comparators first of all.

Q. The final point -- this is my last question, sir -- now, you have been keen to emphasise more than once that there is a guideline threshold of, you say, £20,000 to

£30,000. We disagree on that. Now, let us look at the statistics on approvals and rejections. If we go to {XF3/36/1}, we see at the top, it is the paragraph starting "Cost-effectiveness", it says:

"Cost-effectiveness alone ... predicted 82% of decisions ... There was no evidence that the threshold has changed significantly over time. The model with the highest prediction accuracy suggested that technologies costing £40,000 per [QALY] have a 50% chance of ... rejection (75% at £52,000...25% at £27,00/QALY)."

So to put it another way, on these data, there is a 75% chance of approval below £27,000. Do you see that?

A. 25%, is it not?

Q. Yes.

A. Yes.

Q. That is the rejection, so the approval rate therefore is 75.

A. Oh, the approval, sorry, yes.

Q. Now, we know Dr Skedgel's base case, all of them are below 20,000. When he halves his efficacy estimate he is between 20 and 30, and on the basis of these data, the cost-effectiveness assessment had a 75% chance of approval at those thresholds.

A. So this gets back to the point that my learned counsel

put earlier and put up that figure where it said that even under certain circumstances where they are well within the threshold of £20,000, they may get -- as an individual study, they may get rejected in terms of meeting NICE guidance.

So I think in broad aggregate, you could tell me that this is true. As to whether it is true for a specific study, I would have to look at it and I would come to my conclusions and, having looked at a specific study put forward by Dr Skedgel in terms of whether it is consistent with NICE guidance I would say: well, actually, I would want slightly more information and data to be provided before I could conclude whether or not it is.

MR O'DONOGHUE: Well, we can see the aggregate data, they say what they say.

Sir, I have no further questions.

THE PRESIDENT: Thank you very much, Mr O'Donoghue.

A. Thank you.

THE PRESIDENT: We will have some re-examination. We are going to rise for five minutes because we need to make a call regarding arrangements running past 5.00. We will not run very far past 5.00, but a call does need to be made, so we will rise for five minutes.

(4.57 pm)

(A short break)

(5.00 pm)

THE PRESIDENT: Thank you very much, Ms Morrison. Over to you. Oh I am sorry, we have lost the witness. Well, that is entirely understandable. It has been a long afternoon.

MR HOLMES: While we have this brief intermission, may I raise one point of housekeeping?

THE PRESIDENT: Yes, indeed.

MR HOLMES: It just concerns the timing of written closing submissions.

THE PRESIDENT: Yes.

MR HOLMES: There is provision in your order from November 2022 for them to be provided on Friday afternoon of next week, but it occurs to the CMA at least that that may not give you sufficient time to read and digest three sets of written closings and we, for our part, would also quite like some time to see the other parties' written closings further in advance of oral closing submissions.

With that in mind, we wondered whether the Tribunal would prefer to have written submissions earlier in the week, perhaps on Thursday, but we are very much in your hands.

THE PRESIDENT: Is there an agreed position in terms of the

timing?

MR HOLMES: We have briefly canvassed with counsel, but I think there is a sort of diversity of views. I am not quite sure where everyone has got to.

MR BREALEY: The CMA have not contacted me. I would be very against a Thursday cut-off. The CMA has a team doing their submissions, Ms Stratford has a team doing the submissions. We will be doing the submissions.

THE PRESIDENT: This is obviously controversial. We will finish with Professor McGuire.

MR HOLMES: Sorry, I did not mean to --

THE PRESIDENT: Not at all.

Professor, we are in the final stretch. I will pass you over to Ms Morrison.

A. Thank you.

Re-examination by MS MORRISON

MS MORRISON: I think everyone will be relieved to know that I only have two re-examination questions.

The first one: there was a discussion about *Hydrocortisone* and what your instructions were on that, and you referred in your answer I believe to a passage earlier in your position paper but we did not go to it. I wanted to check that we have the right paragraph that you were trying to refer to. If we could go to {XE6/6/4}, paragraph 13, if we could go over the page to

the next page. You are basically setting out there the issues in disagreement. Is it the final passage? Essentially there is a quote in the middle of this incomplete paragraph, and then you go on to explain what you have been asked to consider in respect of the *Hydrocortisone* judgment. Is that what you were referring to in terms of your instructions?

A. Yes, yes.

Q. Professor McGuire, the last one is you were taken through quite a long list of the abnormalities of competition in the pharmaceutical market, so I just wanted to ask you is there any competition in the pharmaceutical market?

A. Well, there is -- yes. For generics, yes, for sure; branded generics, against generics, yes, but with some product differentiation, and some would argue even in the patented drug market because the patent holds for the chemical entity, and you might get similar chemical entities, and, therefore, there is some competition there.

MS MORRISON: Sir, that was everything I had to ask.

THE PRESIDENT: I am very grateful. Professor, thank you very much for your time and your evidence. You are released from the witness box with our thanks.

THE WITNESS: Thank you very much.

Housekeeping

THE PRESIDENT: Before we go to timing of closings, we have a document to circulate regarding the structure of closings which we will hand round and I will give you a brief explanation as to what it is intended to do and how it hopefully will assist us.

We are not expecting comments on this. What it is essentially is a running order or structure of closings to assist us. It obviously has a structure which is based on how we presently view not so much the answers to the case, we are very far from that, but how we would like the parties to present their submissions so that we have a degree of equivalence between what everyone is saying.

Now, we do not want to impose a straitjacket, so you should feel free to put forward a different approach if that is how you feel you can best serve your clients' interests, but we would want an articulation as to why it is you feel that the questions we have set out are better addressed -- that is to say better for us to reach an outcome -- so that we can understand the difference of views.

We have tried to set something out which will enable everyone to present their case in the best and strongest way. If this structure does not work for you, then we

see real value in understanding from you why it does not work before you go through and do it in a different way.

So if there is tension with this structure then feel free to go down your own route, you are very welcome to, but we would like to know why because it will I think assist us in understanding where the parties are coming from.

Pushback on this is welcome. The reason it has been done in this way is because there is a tendency for each party to plough their own furrow and for us to be faced with, as it were, submissions both written and oral which do not engage with themselves but which pass like ships in the night, and that in our view makes our job harder and not easier.

So it is in that spirit that this document is handed down, but it is something that has been created at a very brisk pace and you should take it with that health warning in mind as well as what I have said otherwise.

Now, turning to the question of timings, if the order indicated a date of Friday we do not think that it is right to impose a different order now if it is not agreed, and clearly it is not agreed, so we will stick with what has been ordered.

If it is possible to produce the documents sooner,

then we will read them with pleasure sooner, but that is no more than an indication that we would be assisted by that, because of course we are confining our reading to over the weekend and weekends should not be solely devoted to the reading of closing submissions no matter how interesting they might be. So we are not going to say anything more than that.

I am reminded that we might impose a length limit. I do not know if we have or not.

MR HOLMES: I do not believe there is one at present, sir.

THE PRESIDENT: I frankly am not keen on page limits. You all know that we will read shorter submissions twice or perhaps three times. If they are long, then they will only get one reading because that is all we are going to have time to do. So I leave it to your good judgment as to how you present matters and how you expand things orally. That is a matter for your discretion.

Before we rise and I adjourn into Monday week, is there anything else that we need to deal with by way of housekeeping?

MR HOLMES: Not from our perspective, sir.

THE PRESIDENT: Mr Brealey, of course.

MR BREALEY: Would we be dealing with -- looking at the (a) to (i), would you want us to do all the law within any particular -- whether it is case 2 or case 3?

THE PRESIDENT: I think the law is built in there --
MR BREALEY: Right.
THE PRESIDENT: -- but, Mr Brealey, please do not treat this as a more sophisticated document than it actually is. It is something that has been put together with some rapidity in light of our thinking having just concluded the evidence. We felt that it needed to be produced now rather than in a couple of days time because of course you will already have been doing some writing and the writing is really about to begin now. So I am not going to expand on this any further.
MR BREALEY: No.
THE PRESIDENT: Infelicities in this document, they are bound to exist. It is simply intended as a way for you to help us, so it should be taken in that spirit.
MR BREALEY: No, I can see the law could be in a particular section.
THE PRESIDENT: It could be in a number of places.
MR BREALEY: Yes.
THE PRESIDENT: We really do not want to cramp your style. What it is is a means of ensuring that we have a kind of parity in terms of the way things are addressed so we can compare and contrast submissions and understand where your points are located. It is no more than that.
MR HOLMES: Sir, just one very brief request: would it be

possible to have this circulated in soft copy so that we can get it quickly round our respective teams?

THE PRESIDENT: Indeed, we will do that when we rise.

MR HOLMES: I am grateful.

THE PRESIDENT: Unless there is anything more, thank you very much for all your efforts on the evidential front. We will resume at 10.30, I think -- is that right? -- on Monday? 10.30 on Monday.

MR HOLMES: I believe so.

THE PRESIDENT: Thank you very much.

(5.11 pm)

(The hearing adjourned until 10.30 am on Monday, 11 December 2023)