Friday, 29th February 2008

(11.00 am)

(Proceedings delayed)

(11.45 am)

MR JUSTICE BURTON: Sorry to have kept you waiting.

MR NASH: You will have gathered that the parties are in discussions.

MR JUSTICE BURTON: I didn't, no.

MR NASH: The parties have been in discussions since last night.

MR JUSTICE BURTON: Yes.

MR NASH: And we both feel that it would be at least worth postponing things until 2 o'clock to see what happens.

It may be that at 2 o'clock we may be coming to you and saying we need a little more time, but we will cross that bridge when we get to it.

MR JUSTICE BURTON: Thank you very much.

MR BEAR: Can I just mention one thing which may have slipped my friend's mind. Professor Sandercock can only be here today and he is here now, having come down from Edinburgh.

MR JUSTICE BURTON: So we may need to take his evidence de bene esse, so to speak, by way of interposition, at 2 o'clock.

MR BEAR: Yes, I think if we haven't got to any --

MR JUSTICE BURTON: If you are not sufficiently close at 2 o'clock then plainly we will have to take Professor Sandercock and deal with his evidence in full this afternoon.

As I said, I will sit until 5 o'clock. If you are within an ace -- I will leave that judgment to you, but that must be an important matter, because clearly if he is ever to give evidence, it has to be today.

MR BEAR: It has, thank you.

(11.47 am)

(The short adjournment)

(2.00 pm)

MR JUSTICE BURTON: Yes.

MR NASH: My Lord, we are continuing, so Professor Sandercock I think needs to be interposed as a witness.

MR JUSTICE BURTON: Right.

MR BEAR: Yes, I call Professor Sandercock.

MR JUSTICE BURTON: Thank you.

PROFESSOR SANDERCOCK (affirmed)

MR JUSTICE BURTON: Thank you, now you can either sit down or stand up, whichever you prefer, or do both, sit for a bit, stand up for a bit.

The most important thing is that you speak up very clearly, as you are doing, because those don't amplify

your voice, they simply record?

A. Thank you.

Examination-in-chief by MR BEAR.

MR BEAR: I hope you have a volume called witness statement 1 to hand; can you go to divider 6 in that?

A. Yes, I do.

Q. Are the contents of that witness statement true and correct?

A. Yes.

Q. And is your address as there stated?

MR BEAR: My Lord, with your permission I would like to Professor Sandercock some questions in chief.

MR JUSTICE BURTON: Yes, certainly.

MR BEAR: As we know, you were and indeed are the Chair of the DSMB in this clinical trial?

A. Yes.

Q. Again, if you could keep your voice right up. It is common ground, I believe, that the data safety monitoring board, when it came to conduct its interim reviews, did not look at what we are calling in this legal trial, the HPM data?

A. That is correct.

Q. Direct your answers to his Lordship, as far as possible?

A. Sorry, my Lord.

MR JUSTICE BURTON: Don't worry.

MR BEAR: The question I would like you to answer and to explain to his Lordship is why the DSMB did not look at the HPM data.

A. In a trial of this nature, the first point is that the HPM database is not assembled for the scientific purposes of the trial, the study in question, but rather to fulfil the regulatory requirements of the drug company, that the relevant -- the competent authorities be made aware of any SUSARS or serious adverse reactions related to the drug, and that has to be conducted within a particular timeframe and because of the number of people that have to be informed, the HPM has a very specified number of things that it must do with these reports.

We were asked as a committee whether we wanted to see that data, or the data from the case report forms, and we elected that our decision-making should be made on the main trial database, rather than the database compiled for regulatory purposes.

MR JUSTICE BURTON: What did you expect, if anything, they would do with the HPM database?

A. The trial co-ordinating centre?

MR JUSTICE BURTON: Yes.

A. Their responsibility is, at the end of the trial, when the process of data collection is complete, to reconcile

the two databases and make sure that they are in complete agreement as to the nature of events, the frequency of events and attribution of the likely cause of the event, whether to the drug or not.

MR BEAR: I asked why you didn't look at the HPM data; what was the data you did look at for serious adverse events, or adverse events, if there is any difference?

A. The important question for the data and safety monitoring committee is not just to look at those events coded as severe, but to look at the pattern of all adverse events for the reasons set out in my witness statement, but the data in this particular sort of trial, where little prior knowledge about the effect of this drug in patients with traumatic brain injury has been accumulated, that one has to keep a very open mind about the likely adverse events that might occur, and therefore one needs to look at adverse events, deaths, serious adverse reactions, and the state of the patient, that is whether they are disabled or not at the end of the treatment period.

So one needs to look at a range of -- pieces of evidence to make a decision.

Q. Where would you find that range of pieces of evidence?

A. No.

Q. Where do you find it?

A. Within the case report form, which -- particularly -- the most informative piece for our decision making was the state of the patient after the longest period of exposure to the drug or placebo which is at 15 days. So if the drug is going to have an effect it is most likely to be seen after the longest period of exposure.

Q. Could I ask you to look in -- before I do that, in the first answer that you gave on -- at page 4, my Lord, of the transcript, at line 20?

MR JUSTICE BURTON: Yes.

MR BEAR: Professor Sandercock said:

"we were asked as a committee whether we wanted to see that data or the data from the case report forms and we elected that our decision making should be made on the main trial database rather than the database compiled for regulatory purposes."

Is there any significance to you as a scientist or clinical trial conductor, so to speak, in the fact that you made your selection at that point?

A. The design of a clinical study works to a protocol and you specify in advance those items of data you will look at, how you will look at them and which items of data you will place greater emphasis upon, and -- so therefore when looking at the structure of the shell tables that laid out the data that we wished to look at,

we took those scientific considerations into the way that the -- into the items of data that we wanted to look at.

Q. Would a DSMB, on occasion, alter the type of data that it had looked at by a decision made during the course of the trial?

A. That could well occur, if, for example, some particular sort of adverse event was starting to occur, some sort of pattern that looked worrying, we might well ask for additional data, and indeed at our first meeting when we discussed the shell tables we felt it prudent to ask for some items of data relating to liver toxicity, and so the shell tables were duly modified.

MR JUSTICE BURTON: Can I just know what your question was there, because it has not got properly recorded on the transcript.

MR BEAR: No, and I'm afraid I'm trying to remember the exact words, would a data safety monitoring board, the gist of it, modify the type of data that that was going to be looked at by a decision made during the course of a trial. I am sure it will come out on the final transcript.

Now, we are going to get close to the point where I need to discuss unblinded information.

MR JUSTICE BURTON: Yes. Can I just ask a question before

we do, unless you were going to come to it, and that is the soft lock. Are you going to come to that?

MR BEAR: It would be very convenient for your Lordship to --

MR JUSTICE BURTON: I was just going to ask, there is a provision for soft lock in the procedures under which this particular trial was being carried out by the TCC, such soft lock to take place at various stages. Did you know that?

A. Yes, we were aware of that, because the materials that had been prepared by the London School of Hygiene, that would be the normal procedure, but -- so we were aware of that, yes.

MR JUSTICE BURTON: Now, did you know that that was altered in some way, and if so, when?

A. We made a request at our second meeting, when we had data on some 40 patients, that we wished to see the data again because they were accumulating rapidly, and that would necessarily mean that a soft lock was not possible. So when we asked for analysis of the data, when data on 100 patients were available, it was an inevitable consequence of that request that no soft lock could be performed.

MR JUSTICE BURTON: You say it was an inevitable consequence; was that discussed? If so by whom, or was

it simply implicit?

A. I think as we are all experienced trialists it was absolutely self-evident to us that was going to be the case. We wanted the most up-to-date set of data that was available and a consequence of that was that it would be necessarily not as complete as had more extensive data cleaning taking place.

MR JUSTICE BURTON: You mentioned, indeed you were told by Mrs~Shakur that it wasn't fully cleaned. Did you appreciate that meant that the soft lock procedure had not been gone through?

A. Yes, it is obvious.

The other point to make is that in the reports that were submitted to us, the first page very clearly sets out the provenance of the data, how it has been accumulated, exactly in whom data is available at what stages during that progress through the trial. So, it was very clear to us what the potential -- what exactly we were looking at.

MR JUSTICE BURTON: And there is a reference to four missing values, I think, in the report; did you notice that?

A. Missing values are -- would again be entirely to be expected, given the way that we had requested the data, and that was not a surprise to us.

MR JUSTICE BURTON: Did it make any difference to your

ability to form a judgment?

A. No.

MR JUSTICE BURTON: You want to clear the court of those --

MR BEAR: There is one document I think I can hand up which your Lordship has not yet seen, which is not, I believe, unblinded.

MR JUSTICE BURTON: Yes.

MR BEAR: Can a copy be given to the witness as well?

My Lord, Professor Sandercock, when I met him this morning, showed me this page, which, he will tell you what it is. It seems to me that although in his possession rather than my client's, it should be before the court, and he thinks so as well.

MR JUSTICE BURTON: You have seen this, Mr Nash?

MR NASH: Just now, my Lord.

MR JUSTICE BURTON: Yes.

A. So this is the front page of the analysis plan prepared by Sealed Envelope, Tony Brady, which is very important for the data monitoring committee's considerations because they need to understand when the data accumulating -- for example the data on the patients as they enter the study, will always be much more likely to be available than events that occur at 15 days or subsequently, and so this just explains that of the 216 patients that have been randomised in the study,

baseline forms were not available for 71, 140 were available for analysis, split across the different dose groups, and a complete data set was available on 99 patients. Now, the reason for that is that enables the committee to understand how much data is in process, and that helps us in our decision-making, as to, as it were, how much data -- sort of -- as yet unknown but will be available shortly.

MR BEAR: I don't know whether this could be put perhaps behind Professor Sandercock's witness statement.

MR JUSTICE BURTON: Yes.

MR BEAR: Would you mind putting it at the back of the divider, Professor Sandercock.

MR JUSTICE BURTON: Now, we are going to have an explanation of his annexures, that is right, to his witness statement?

MR BEAR: I was going to take him briefly to those and I was also going to ask him about his letter of 1st November.

MR JUSTICE BURTON: Well the letter of the 1st November doesn't need to -- or does it, need to have the court cleared?

MR BEAR: I think it would be prudent.

MR JUSTICE BURTON: The court must be cleared of everyone who is not in on the unblinded data, or who is a legal adviser. Thank you very much.

MR BEAR: Yes, well, Professor Sandercock, perhaps we could start with the tables at the back of your statement.

A. Can I make one point of clarification?

Q. Yes, of course?

A. In my original statement that you have, I think, my Lord, I have made some typographical errors in the preparation of the table and these have been corrected.

MR JUSTICE BURTON: We have a substitute version.

A. Yes.

MR BEAR: That was table 2C, was it?

A. That's correct.

Q. If you could briefly explain to his Lordship each of tables 2A, 2B and 2C, and what you consider they show?

A. Okay, these tables are taken from the second interim report from Sealed Envelope, these summarise the key items of data that informed our decision making. We obviously reviewed all of the data, but these are, in our view, the most decisive pieces of information.

The first trial period, table 2A, describes the number of patients with at least one serious adverse event, and this is the most important -- this is the analysis of serious adverse events, which is the most meaningful in terms of trying to understand the effects of the drug. So this is -- you will see that in those allocated the high dose treatment, 29 per cent had at

least one serious adverse event, on the medium dose 43.8 per cent, on the low dose 28.9 per cent, and those allocated to placebo 10.3 per cent.

So the first point is that in all of the treatment groups the frequency of adverse events, serious adverse events, was -- sorry, the frequency of patients with at least one serious adverse event was higher.

The shell tables also required an analysis of all the treatment groups combined, compared with placebo, and for that we saw there were 34 allocated drug and 4 allocated placebo. That is 33.7 per~cent against 10.3 per cent. That is roughly a three-fold excess of patients with at least one serious adverse event. So that is one piece of data that suggests that the treatment is not beneficial, and potentially harmful.

Q. Before you go on to 2B, can you tell us about the bottom part of your table, the relative risk and the note?

A. One of the statistical methods to describe the effect of treatment is to use a measure called a measure of relative treatment effect, that is called a relative risk, which compares the frequency in the two treatment groups, and it is a ratio and 3.28 in rough terms is, it is a three-fold excess of treatment.

The lower and upper confidence intervals are statistical measures of the precision with which one can

make that estimate of the relative excess, and the precision of the estimate is influenced by the number of patients that have been analysed, so the greater number of patients the greater the precision, and so the lower estimate of 95 per cent confidence was the treatment increase, the risk of at least one serious adverse event by about 25 per cent, or it could have been up to about a seven or eight fold increase in risk.

Q. What does "P" mean?

A. P is a statistical term and I am not an expert statistician so, in simple terms, if P is less than 0.05, this expresses the probability that this is unlikely to have arisen by chance. It is not a -- a statistician would not approve of that description, but essentially P less than 0.05 means it is unlikely to have arisen by chance.

Q. What is the number here?

A. Less than 0.05 which is again even less likely to have arisen by the play of chance.

Q. Could one express 0.05 in a different way?

A. Statistically significant -- what other forms of words one could use ...

Q. Could I put it to you, is it or is it not the same as five in a thousand, or is that the wrong way to look at it?

A. It is not quite the correct interpretation. All one can say -- it is five in a thousand indeed, in numerical terms, it just means it is unlikely to have arisen by chance. And certainly when you get down to 0.05, 0.005 or 0.001, then these are results that one has to place considerable emphasis on.

Q. Why is that?

A. Because the play of chance can have a very major effect and the statistical significance is a way of making sure that the play of chance is not influencing the results unduly.

Q. Right?

MR JUSTICE BURTON: Now, you didn't have the -- and had asked not to have -- the other database. If you had, it is possible that you would have seen that according to the HPM database, there were more SAEs, 92, say, rather than, say, 59, across the board, through all the four groups in -- at any rate so, far as we are concerned, blinded form.

Of course you knew that you didn't have that, and you were arriving at your conclusion knowing that. So did you allow for the possibility that there were more SAEs than were shown here, if in fact there had been a reconciliation of that database?

A. Yes, because we knew there were more data coming all the

time, so the important thing is to look at these data in a context, and the context is provided by the other aspects of information that come from the CRF, because, as I explained, the CRF summarises what the patient is like at 15 days after the period of maximum exposure to the drug, and so if you look at the status of the patient at 15 days with the other information on the CRF, that, if you like, gives the most complete context into which to view an analysis at any given time of the likely frequency of serious adverse events between the different treatment groups.

If you just look at the HPM database at any one moment, you will not have that other information contemporaneously with it, and you have much less context in which to view that.

MR JUSTICE BURTON: What would have been the case if -- and you are assessing this without that information because you have asked not to have that information -- there had in fact been less SAEs right across the board, because you couldn't know where they were, than were here apparent.

A. Could you repeat the question again, my Lord?

MR JUSTICE BURTON: Yes. Here you didn't have this information, had you had it, it might have shown that there were less SAEs than had been reported in the CRF?

A. Yes.
MR JUSTICE BURTON: And you hadn't asked for them, so you knew you didn't have them.
A. Yes.
MR JUSTICE BURTON: Is it a relevant mindset, but if it is, can I ask you in any event to adopt it for the moment, to say to yourself well, if there are in fact less SAEs, if the reconciliation were done, which we haven't had done, across the board, would that have made any difference to your conclusion?
A. If the serious adverse events had been evenly distributed across the treatment groups -- that is, there was no clear evidence that the treatment was harmful -- then a slightly smaller number of adverse events wouldn't have made any material difference.

If, as we observed in this particular analysis, there were more serious adverse events -- there were more serious adverse events in the treatment groups as compared with the placebo groups, but there were just rather fewer of them, then the main effect that would have had, that is the distribution between the treatment groups, was approximately the same.

What would then happen is that the confidence intervals would be rather wider, but the relative estimate of treatment effect would be approximately the

same. So we might still observe a three-fold excess, but the confidence intervals would perhaps be wider.

Now, that of itself would not necessarily have altered our decision making because, as we said, in adhering to our guiding principle that we had to look at the pattern of events, we had to look at everything, not just the frequency of serious adverse events. That was not the sole decision-making criteria.

MR JUSTICE BURTON: Yes.

MR BEAR: Could I perhaps follow up his Lordship's question in a slightly different way. Could you be given chronological bundle 12, C12/3447. You will be shown it in just a second, Professor Sandercock, but this was a letter sent to you and your colleagues on December 3rd by Xytis.

A. Yes.

Q. You will see in the third paragraph it says:

"We presented the HPM table ..."

I should read the first paragraph:

"Concerned there may be significant discrepancies between the SAE data set prepared and presented to your committee in official pharmacovigilance SAE database ..."

And then they refer in the third paragraph to presenting the table of serious adverse events and

deaths to Dr Gudkoep, who is a Xytis representative:

"He was surprised by the HPM data set that was very different from the DSMB ..."

That is the extract that was given by you to the TSC, and then there is reference in the table, as you can see, to the HPM database, second line of the table:

"Number of SAEs: total 49."

Then they put a question mark --

MR JUSTICE BURTON: We know it was 94, where the question mark --

MR BEAR: We know it was 94 and whether or not anyone else knew doesn't matter for the purposes of this question --

MR JUSTICE BURTON: The question mark can now be replaced with 94.

MR BEAR: Yes.

MR JUSTICE BURTON: And 38 in the next one down.

A. Thank you.

MR BEAR: Now, did you receive this letter?

A. Yes.

Q. Did it cause you and your colleagues to reconsider the decision that you had reached on November 1st?

A. I forwarded this email immediately to my colleagues, Professor Rogers and Professor Stephen Senn,because I thought we should reach a joint decision on this letter, which was clearly very important.

We were unanimous in our view that the small discrepancies between the different databases would not materially alter our decision. We were quite clear about that.

Q. Does that include the 94 that we have been talking about?

A. Yes, because we had looked at those data just immediately the day before.

Q. This is December 3rd, not November?

A. Sorry, I beg your pardon, but we were very familiar with the numbers of events, having spent some time discussing them.

Q. So did you feel that there was anything that needed to be done as a result of this letter?

A. We took the view that this complaint related to events which were outside our field of vision, outside our terms of reference. This related to the data that were sent to us, we had made it clear that our decision-making process was on the data that we had requested, and we therefore felt that any differences between these databases did not materially affect our decision making.

Q. Does that answer your question?

MR JUSTICE BURTON: It may be that just for the future you may like to write in 94, 38, 42, 3, 11, 37.

A. Thank you, my Lord.

MR BEAR: I had distracted you from the exposition of your table so, could we go back in your witness statement to table 2B, please. Again, if you could just explain to the court what that means to you and what it meant to you and your colleagues?

A. Table 2B describes an analysis of two scales that report the status of the patient at 15 days. These scales have a few points on them. The Hireos scale is the one which goes from 0 -- which means no symptoms at all -- down to 5, which is quite disabled. So it is a summation of the patient's clinical state, which is extremely useful. The DRS is the disability rating scale, which is a different measure, but again summarises the patient's clinical state at the end of -- at that particular moment, and these were measured at several points during the trial, but the one we were most interested in was at day 15.

So for both of these scales, if the patient has a low score that is good, and if they have a high score, that is bad.

What are presented here are the averages, the average scores for each of these two scales, and you will see that if we look at the DRS, amongst those with the high dose they have a high score, and those on

placebo progressively through the doses get down to a low score, and similarly with the Hireos scale, that on average, patients allocated to one of the Anatibant treatment groups had higher Hireos scores than those allocated to placebo, and in the case of the Hireos scale that difference was statistically significant.

MR JUSTICE BURTON: This is on the basis of the information in the CRF?

A. Yes.

MR JUSTICE BURTON: How far is it dependent or reliant on the number of SAEs?

A. Not at all. It is a completely separate measure. And in a sense, if you like, it is more important than the SAEs, because it, you know, a patient might experience an event that is -- that doesn't influence their, for example, if they develop a blood clot in a leg vein, that is a important medical condition but if it is treated appropriately it may not affect their status at 15 days, and so it provides a summary of whether the patient is ill or well, if you like.

MR JUSTICE BURTON: Yes.

A. And so to a doctor, that is, in a sense, more important than just -- and to the patient, is more important than anything else.

MR BEAR: Table 2C.

A. Table 2C describes the frequency of deaths between the different treatment groups, and again, as you can see, the frequency -- patients were more likely to die if they were allocated to one of the Anatibant groups, although this -- and there does appear -- there is no clear dose trend, but the frequency was higher when we combined all of the groups, although this did not achieve statistical significance.

Q. How much higher was it?

A. The relative risk was 1.47, which is approximately 50 per cent higher, and that is certainly a very worrying trend in the accumulated data, particularly when viewed together with the disability data, the Hireos and disability rating scales.

Q. Can I ask you to consider the following hypothetical question, and if you can't answer it, say so, and if you can, do.

Can you hypothetically assume that you had had before you the data that you summarise in table 2B, and the day that you summarise in 2C. So, the Hireos and disability data in 2B, as is shown, and the death data in table 2C, that you hadn't had any trends emerging on a comparative assessment of SAEs. Do you follow that scenario?

A. I do.

Q. Are you in a position to say what you think you and your colleagues would have done in that situation, and to give reasons for it, if you are in that position?

A. If I might just digress a moment, my particular interest, apart from head injuries, is with patients with stroke, and one of the most important aspects of stroke is: are you either dead or do you need help from other people in your daily activities? So the combination of being either dead or needing help, that is scoring 4 or 5 on something like a Hireos, is a medically important assessment of the effects of treatment, and I think -- although of course we are talking about a hypothetical situation, I think if we had seen a non-significant increase in death but a clear trend, a significant trend that was adverse for Hireos, we would have had to give very serious consideration to stopping the trial and we could well have decided, had the serious adverse events been evenly distributed, still decided to at least suspend recruitment while we could assemble as much data as possible before making a final decision about the trial.

MR BEAR: Thank you very much indeed. I don't have any further questions, so could you wait there.

Cross-examination by MR NASH

MR NASH: Professor Sandercock, at the beginning of your

statement, you tell us that you were a principal investigator for the CRASH 1 trial; that is right, is it not?

A. That's correct.

Q. Is it right that Professor Roberts was the chief investigator on that trial?

A. That is correct.

Q. So presumably prior to becoming involved in the BRAIN Trial you had worked closely with Professor Roberts in CRASH 1?

A. I had.

Q. And you knew each other well?

A. Yes, we knew each other, principally as scientific colleagues, I don't have -- I know him, but, you know, we live a very long way apart.

Q. Can I show you, please, the protocol for CRASH 1. (Handed).

It has probably been some time since you looked at this, I suspect, Professor Sandercock. One or two questions arising from it. If you look at the first page, please, it has a summary of the trial, and what is described there is that millions of people are treated each year for severe head injuries, a substantial proportion die and many more are permanently disabled:

"The short term caustica steroid infusion can be

reliably shown to reduce these risks by just a few per cent, then this might have affect the treatment of a few hundred thousand patients a year, protecting thousands from death or long-term disability."

So the purpose of this trial was not to test a new treatment, that's right, isn't it?

A. Correct.

Q. It is to test the efficacy of a widely-used existing treatment?

A. That's correct.

Q. And you go on within the summary in the third paragraph, fourth paragraph:

"To detect or refute improvements of only a few per cent in outcome, many thousands of acute head injury patients must be randomised between control and steroid infusions and such large numbers will be possibly only if hundreds of doctors and nurses can collaborate in the participating emergency departments."

So the structure of this trial was to test the efficacy of an existing treatment through many, many thousands of patients?

A. Correct.

Q. And the reason why you needed many, many thousands of patients was to produce a reliable statistical measure of efficacy?

A. That's correct.
Q. Can we go on through this, please.
It is headed "Trial protocol study design"?
A. Yes.
MR JUSTICE BURTON: Yes, he has it.
A. Yes, I have that.
MR NASH: And perhaps you would just like to remind yourself of the summary.
A. Yes.
Q. The procedure for this trial was a relatively straightforward one, is that correct?
A. Yes.
Q. The patient was selected, and having been selected, his or her progress was monitored with either a placebo treatment or the caustica steroid?
A. Yes.
Q. And at the end of the treatment period a form was to be sent in by the treating clinician, correct?
A. Yes.
Q. And we see that form, I think, at the back, three pages in?
A. The early outcome form.
Q. Yes clinician.
And the choices for the clinician filling in this form are very limited, aren't they? In paragraph 4, you

have an outcome with a ticking box system, a date to be given, a transfer if necessary, and then a series of boxes against (d), no symptoms, minor symptoms, some reaction, dependent, fully dependent, and then dead. So that is what you have to choose with your patient?

A. Yes.

Q. So compared to the CRF procedures which we have in the present BRAIN Trial this is a much more simple assessment exercise; do you agree with that?

A. Well, the two primary scales for the assessment of the patient's state are the same, that is, no symptoms, up to dead. So those two elements of assessing the state of the patient are exactly the same.

Q. But this trial didn't require an assessment with the Glasgow Coma Scale or the Hireos scale?

A. The Glasgow Coma Scale was measured at the entrance to the study.

Q. But it did not require an assessment at the end of the study or a report?

A. That was not a pre-specified part of the protocol.

Q. No. And the clinician was not required to monitor the incident of serious adverse events during the study; that's correct, isn't it?

A. That is correct.

Q. And it follows from that, of course, that he wasn't

required to attribute the causality of serious adverse events during the course of the study?

A. Yes, that is correct.

Q. Do you recall now whether there was a remote terminal link between the individual assessment centres, the individual clinics, and the trial co-ordinating centre in this trial?

A. I would need to discuss that with Dr Shakur again. It is some time ago now. To my recollection, they were certainly beginning to develop the process of collecting data over the internet, but I would have to look -- I mean, I have been involved in so many trials since then I would have to check with exactly the process of data collection.

But such a simple system of data collection is not unusual in large-scale trials.

Q. I'm not suggesting it is, what I am suggest something that the BRAIN Trial was in fact a rather complex trial so far as data collection is concerned. It required many additional items of data, additional to those sought in the CRASH trial; do you accept that?

A. Yes, but in a smaller number of patients. So the load of data -- does one consider it more complex to deal with data from 20,000 patients from a large number of countries, or a small number of patients from a small

number of countries? The data management tasks are equally complex, they are just slightly different.

Q. Well, the data management within the BRAIN Trial required the collection of many items of different data relating to the patients, which required clinical judgment at local level, both as to the causality of serious adverse events; do you agree with that?

A. The investigators were asked to give their opinion about the causality of serious adverse events, but since they were unaware of whether the patient was on the active drug or the placebo any estimation of causality is not likely to be reliable.

Q. By causality we are not talking about whether or not they are reacting the drug, we are talking about whether or not their serious adverse event is attributable to their existing condition, traumatic brain injury; you understand that, don't you?

A. But they are also asked to make a comment as to whether they believe it to be due to the study drug.

Q. Certainly, and that is additional item of information and clinical judgment that has to be deployed, isn't it?

A. Yes.

Q. And in addition to that, they have to assess progress through the various impairment scales that are being used during the course of the treatment; that's right,

isn't it?

A. That's correct.

Q. And then all of that information has to be fed up to the trial co-ordinating centre on days 3, 6, I think 9 and 15 of the course of the trial; that's right, isn't it?

A. That's correct.

Q. So in CRASH 1 you have a simple form that is sent at the end, with limited number of items of information. In BRAIN, you have a great many more items of information that have to be fed in at regular intervals during the course of the trial?

A. That's correct.

Q. Did you tell us that Mrs Shakur was involved in CRASH 1?

A. She was.

Q. Did she occupy the same position in CRASH 1 as she did in the BRAIN Trial?

A. I would say she had many roles that were similar.
I think I would have to defer to Professor Roberts as to the precise content of her job. Her role was to make sure that in relation to my activity as Chairman of the data monitoring committee, was to make sure that the data monitoring committee took place when it was planned to and that we were supplied with what we requested.
But I -- at that point -- was not -- that was my main interest in Mrs Shakur, that that function was

fulfilled.

Q. Can we then turn to the BRAIN Trial and have before us the protocol for the trial, which you will find in the first core bundle, behind tab 3. It is right, is it not, that you had the opportunity of considering this protocol before you began your function on the DSMB, before you began to chair the DSMB for the trial?

A. That's correct.

Q. That would be perfectly normal with this prosecute set for the trial.

Would you look, please, at page 284 of the protocol set for the trial.

Under "Objectives" there are two matters identified, what is called a primary objective, which is safety, to evaluate the safety of different doses of Anatibant; yes?

A. Yes.

Q. And secondary objective is:

"To assess the effect of Anatibant on mortality, morbidity among patients with acute traumatic brain injury, mortality will be assessed 15 days following post-injury using the Glasgow Coma Scale, DRS and clinical scoring system that has been shown to be strongly correlated with functional outcome at six months post-injury (the Hireos scale) and then finally

to assess PK [which I think is pharmokinetic] profile ...?

A. Correct, yes.

Q. "... in a larger profile of patients."

It is clear from this, isn't it, that one of the objectives of the BRAIN Trial was, so far as possible within a small population, to assess efficacy?

A. No, it was there to assess safety and that was our prime concern. To ensure the safety of the participants in the trial. In any trial, you specify a primary outcome or a primary objective, and to my mind this statement under the first bullet point, to evaluate the safety of different doses seems remarkably clear.

Q. I am pointing your attention to secondary objective, which is stated to be to assess the effect on morbidity using those scales, and those scales are concerned with the efficacy of the treatment; do you accept that?

A. Yes. Those scales can also be used to assess the hazard of treatment.

Q. I suppose it depends which way the results come out?

A. I think it is fair to say that data monitoring committees look at measures of outcome as assessments of the effect of treatment, so one cannot presuppose that this treatment will reduce disability. If it increases disability then it is not a safe drug.

Q. It is a simple point, I think, Professor Sandercock; one of the objectives of this trial, in addition to safety is to assess the efficacy of the drug --

A. Can I interrupt?

Q. Of course?

A. As you have pointed out, to establish the efficacy of the trial requires a very large number of subjects. But before one is to expose 10 or 20,000 patients to the risk of a new drug one does need to assure one's self -- within reasonable limits -- that it is safe. And that was the purpose of this study: before going on to very large-scale trial which might reliably establish whether this saves lives or reduces disability, one would want some indication that there was a reasonable probability that it would turn out to safe. That was our judgment -- that was what we were charged with, to decide whether, in the light of the evidence that was accumulating, whether there was a reasonable probability that this drug would turn out to be safe.

MR JUSTICE BURTON: Where does the secondary objective fit in on that basis?

A. To assess the effect, it doesn't presuppose that it is beneficial or harmful. It just says:

"These are the ways we will assess the effects of this drug. "

It doesn't say efficacy, it says "effect", and an effect may be positive or negative. And one cannot, in designing a scientific experiment, pre-judge what the results will be.

MR NASH: I am not suggesting you pre-judge, Professor Sandercock, but clearly if the assessment through the coma scale and the Hireos is positive, that would suggest that within the limitations of the small population that the drug is beneficial; that's right, isn't it.

A. That would be a reasonable assumption.

But again, with a small number of patients one would need -- the pattern of events, one would need to be reassured that there was evidence of any increase in the risk of death and that there was no uneven distribution of serious adverse events. With these small numbers one has to look at the pattern of all of the measures and not place undue emphasis on one particular part of the data.

MR JUSTICE BURTON: Is it a limitation of efficacy, if it is anything to do with efficacy at all, to consider the effect on mortality, morbidity, among patients. Is that the totality of efficacy, or is it a subcategory of efficacy, the effect on mortality and morbidity?

"Mortality would be assessed 15 days following the

injury, in hospital morbidity would be assessed [again] 15 days later."

A. It is a statistical point, but if one has a composite measure of outcome, that is morbidity plus mortality, and one -- let's say one has a measure of dead or dependent, one would need to know that the trends both for death and for being alive and free of dependency were both in the same direction.

One would need to be very cautious that for example treatment did not increase the risk of death, but -- sorry -- so that the trends in both death and survival, free of dependency, were both in the same direction. So it is a question of looking at the pattern.

MR JUSTICE BURTON: And you use the Glasgow Coma Scale and the disability rating scale, and Hireos, for that secondary objective?

A. But also taken together with death, because, you know, you can't ignore death. Even though the numbers were not large enough to provide a reliable assessment of the effects on death, we know from the CRASH 1 trial that you need much larger numbers for that, but what we were seeing was not reassuring of safety, and therefore we had to decide that we needed to see the complete data, that is suspend recruitment, collect all the data on the 200 odd patients that had been recruited, which would

increase the amount of information available to our decision making by about 75 per cent. And that was why we made -- that was the basis for our decision, that we should not expose further patients to the risk of this unproven drug until we had seen more data, and more data we knew would be available if those patients which had been randomised but not yet followed up could be put in the database, and we could make a more reliable assessment of whether this drug was, as would appear to be the case but not beyond all reasonable doubt, unsafe.

MR JUSTICE BURTON: And that has not happened because of the suspension of the recruitment and coupled with this litigation.

A. Correct. This litigation has delayed us finding out whether this drug is safe or not.

MR NASH: I will not start straining to what is going on at the moment, but as I understand it, the data is being cleaned.

A. After a long delay.

Q. It is being cleaned now?

A. There was a considerable delay which was not -- sorry. My understanding of the process and the influence of the legal process on the collection of data in these patients was that it did introduce a delay in ascertaining the outcome among these patients.

Q. We may come back to that, Professor Sandercock, but I don't want to spend too much more time on this page, but can you agree with this? That a sponsor of this trial, a trial with this structure and these objectives, could reasonably hope that the assessment of the effect of the drug might give a positive signal that the drug has a positive benefit?

A. Such a signal might be unreliable.

Q. Certainly, statistically it would not be a signal on which you could build a great deal of reliance, because of the small population. But it would nevertheless be a reasonable expectation that this drug might produce a positive signal?

A. It is plausible, but that was not the purpose of this study.

Q. Can we move on, please, Professor. Lock at page 298.

At the top of the page, under paragraph 7.5, there is a reference to blinding:

"None of the persons directly involved in the conduct of the trial would have access to the treatment codes ..."

Then there is an emergency procedure.

It is right, is it not, that the blinding parameters which were established for this trial required that the local clinician remained blind to the placebo or

treatment being applied in this case; that is right, is it not?

A. That's correct.

Q. Also the local CRA involved in collecting the data and transmitting it to the TCC?

A. Correct.

Q. And the persons at the TCC who are processing the data, putting it into the database, preparing it for the DSMB, all of those must remain blind?

A. That's correct.

Q. Persons who are involved in the trial but who are not directly involved in the gathering and sorting of data do not require to be blinded. That's right, is it not?

A. I'm sorry, I don't understand the question.

Q. If you are involved in the trial but you are not directly concerned with data management and data handling you are not required to be blinded under the terms of this protocol?

A. That is a very strange assertion. I mean the standard practice in any randomised controlled trial is that the data remain remains strictly confidential to all but the data monitoring committee and the trial statistician who prepares the reports.

Q. Well, I am reminding you of the terms set out in the protocol, Professor. None of the persons directly

involved in the conduct of the trial are the blinded persons. That is what the protocol required, isn't it?

A. Yes, but it makes no statement about other individuals. So, the assumption is that if the people most directly concerned with the trial then everyone else should as well. It is well known in the field of trials that if the results of a trial are released prematurely this may lead to very inappropriate decision making.

Q. The protocol defines the parameters and structure of the trial, doesn't it?

A. Yes, it does.

Q. And the blinding parameter is defined by paragraph 7.5, isn't it?

A. Yes, in relation to the people working with the trial, but the fact that it doesn't specify that persons not associated with the trial can be given access to the blinded data -- I mean, in the field of clinical trials that would be a completely absurd suggestion. I mean, forgive me, but, you know, in my daily practice, doing clinical trials as I do, it is a serious breach of trial conduct, and this is taken as a given amongst the community of clinical trialists, that blinded trials should remain blinded and the data should be retained as blinded until the conclusion of the trial, or until such time as the data monitoring committee and steering

committee decide otherwise.

Q. I don't think there is any dispute, Professor, that the trial should remain blinded. What we are debating is what that means, exactly, and I'm suggesting to you that the provisions of the protocol tell us what that means, and that means that people directly involved in the conduct of the trial are required to remain blinded, and that is the limit of it?

MR JUSTICE BURTON: To what issue does this go, Mr Nash?

MR NASH: It goes to some of the procedures we have been using in this trial, my Lord, to keep people out of the court.

MR JUSTICE BURTON: But I thought we have all done that by consent, haven't we?

MR NASH: It also goes to the question of the reasonableness of the documentary request, because your Lordship will recall an issue about that.

MR JUSTICE BURTON: Right, okay.

MR NASH: But I will move on, because I know we have limited time, Professor.

Page 305 of the protocol. Just briefly as to the procedures:

"Complete physical examination to be done [I said day 9, but it is actually 1, 3, 6 and 15] and abnormal findings to be reported.

"Mortality [at paragraph 8.2], a death information report form in the CRF must be completed. This will record date, time and cause of death. Cause of death can be recorded from autopsy reports. Any death should be reported in the SAE form."

Yes?

A. Yes.

Q. But then that is subject to a loss, if we go over the page at 306. The definition of adverse events, bottom of the page:

"An adverse event is any untoward medical occurrence in a patient or clinical investigation, the subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study drug."

And then over the page, at 307, again dealing with the question of untoward, the paragraph in the middle of the page:

"The above definition of an adverse event in the context of a critical care setting excludes all medical occurrences which are expected in the course of the natural history of traumatic brain injury which are known to occur in reasonable diagnostic or therapeutic procedures. A systematic collection of all occurrences in an emergency set-up would include symptoms

originating from the underlying TBI and from routine procedures, leading to an artificially increased number of events.

"The indiscriminate compilation of both these occurrences and the AEs as defined above could subsequently bias the safety analysis. Therefore this approach is considered as the optimal way to collect the relevant safety data."

Now, what is being said there in lay terms is that you expect traumatic brain injury patients to have many serious adverse events just in the course of their injuries, correct?

A. That's correct.

Q. And you are excluding them because they will skew the data, they will make the trends more difficult to detect?

A. Skew the data in what sense? I'm not sure I understand the question.

Q. Well, I'm focussing on the particular sentence:

"The indiscriminate compilation of both these occurrences and the AEs as defined above could subsequently bias the safety analysis."

A. It would only bias the safety analysis if there was differential reporting between the treatment groups. Bias is the systematic reporting of events to a greater

extent in one group than another.

Q. But there are many factors that might lead to that result, aren't there, Professor?

A. There should be no bias in the reporting of events if the reporter is unaware of the treatment allocation. Bias is introduced if the treating doctor is aware that this patient is receiving the active drug. If there has been significant unblinding and the doctor treating the patient believes that the drug is hazardous then they might be more likely to report adverse events in one group than another, but if the doctor is blinded then there is no bias between the different treatment groups.

Q. When saying that, you are referring to intentional bias on the part of the treating person?

A. No, such biases are known to occur in clinical trials, they are not deliberate, they are unconscious, they occur. It is well understood. They are not deliberate or fraudulent.

Q. If you have a situation, Professor, where you have a doctor in a particular site who takes a more liberal view of adverse events than a doctor in one of the other study sites, he thinks that all adverse events, whether or not they are untoward, ought to be reported within the context of this trial, his results will introduce an inconsistency into the data which has been introduced

into the trial; that's correct, isn't it?

A. If the frequency of reporting of adverse events differs from one centre to another, between one doctor to another, again it doesn't make a difference to the assessment to the differential accumulation of adverse events between the different treatment groups.

Q. If the effect of randomisation is that the doctor who takes a more liberal approach happens to receive more patients to whom the drug is administered rather than the placebo, then clearly that is going to skew the result?

A. No, because the randomisation makes sure that that particular doctor's treatment patient allocation is roughly equal.

Q. By the time that you have recruited the entire trial population?

A. No. The design of the clinical trial is such that as the data accumulates one seeks to ensure balance throughout the trial. For otherwise the analyses of the data monitoring committee, if there was substantial bias in the type of patients recruited into each of the treatment groups, if, for example, there was a systematic tendency to recruit more severe patients into the placebo group, then that would mean that the placebo group would appear to do worse, and would bias

in favour of treatment.

So clinical trials are designed to ensure that patients of equal severity and equal type have an equal chance of being allocated either treatment.

Q. Can we move on through the protocol, Professor Sandercock. If we go to page 308, the definition of serious adverse events, 8.3.2:

"Serious adverse event is a subset of adverse event for the purpose of this protocol."

That's right, isn't it?

A. That's correct.

Q. So in order for something to count as a serious adverse event, it must be both serious within the definition there, and not expected to arise in the course, in the normal course of TBI; that's right, isn't it?

A. In the definition here, expectedness is not part of that definition, if I read this correctly.

Q. No, that is right. But the serious adverse event is a subset of adverse event, which is defined as an untoward medical occurrence. You agreed with that I think a moment ago?

A. Yes, but it can be expected. I mean, death is a serious adverse event and deaths can be expected after traumatic brain injury.

Q. The whole structure of this trial, as we saw a moment

ago from the definition of adverse event, is to try to exclude from the data the expected medical consequences of TBI that, is what it says?

A. The way that the data monitoring committee do that is by looking at the frequency of these adverse events between the different treatment groups. So it is not the attribution of cause to single events, because it may be very difficult, in the context of a patient who has got multiple problems after a severe injury, to decide why they died. But if it happens that the deaths, or one particular sort of adverse event occurs more frequently in one group than another, that is what leads to a reliable medical conclusion about the likely cause.

Q. We are going to come on to those tables in a few minutes, but at the moment I am just trying to establish with you the structure of the trial by looking at the protocol document. What I am suggesting to you is that an SAE, as well as an AE, is required to be an untoward adverse event, for the purposes of this trial?

A. Yes, okay, I accept that.

Q. Thank you.

Page 313. The safety evaluation provisions under 9.2.2:

"The primary analysis: we will test the statistical mall hypothesis that there is not increase in proportion

of patients with at least one serious adverse event in those receiving the drug."

And that is described as the analysis which is to be performed for the purpose of this trial; that's correct, isn't it?

A. That is what is described as the primary analysis.

Q. Yes. And if we go to page 316, we are told that data management, top of the page, is to be performed under the responsibility of the trial co-ordinating centre, and according to its SOP?

A. Yes.

Q. Had you seen the data management plan as part of the documentation you considered when you joined the DSMB?

A. We had been shown the SOP for reporting of serious adverse events and the general structure of the management of the trial was laid out in the protocol. But there are more detailed technical documents which a data monitoring committee would not normally look at, and to my memory I don't think we saw those.

Q. If you go back, please, to page 282, to see how your role is defined within this protocol.

Your membership is identified, the point is identified that:

"A higher risk of morbidity is expected and so to provide further protection the DSMB is set up. The DSMB

will review on a regular basis accumulating data from the ongoing trial and advise the steering committee regarding the continuing safety of current participants and those yet to be recruited, as well as reviewing scientific merit of the trial."

And it then goes on to refer to the DSMB operating procedures.

So your role within this protocol is to monitor safety. It is also to monitor the quality of the data, isn't it?

A. In as far as a data monitoring committee is in a position to do so, given that we are presented only with tabular data.

Q. Can you go, please, to tab 6 in the same bundle?

A. So, if I could just clarify, it would not be normal practice for data monitoring committee to audit the data management systems of a clinical trial that they have been asked to act as independent data and safety monitoring committee.

Q. I am not suggesting you had to audit it, Professor --

A. Otherwise it would be difficult to assure the quality of the data.

Q. If you go, please to tab 6 within the bundle.

This is your charter, these are your rules of operation, as it were. Broad statement of the aims

appears at the bottom:

"Examine the safety data accumulated and insure the benefit/risk ratio remains acceptable.

"Primary responsibility to identify interim analyses of outcome data."

And then "specific roles" over the page:

"The DSMB will review the progress of the trial including updated figures on recruitment, data quality and main outcomes of safety data."

And then:

"A selection of specific aspects could be compiled from the following list. Assess data quality including completeness and by so doing encourage collection of high quality data."

So it is clear, isn't it, that one of your functions was to form a view of the quality of the data which was coming up from the trial?

A. Correct. But based on the data that was presented to us, not by analysis of the database.

Q. And the way that was to be done, if you go to page 1389, please. Describing what the open session would consist of. The open session:

"Accumulating information relating to recruitment and data quality (eg data return rates, treatment compliance) will be presented. Safety details based on

pulled data will be presented and total number of events for the primary outcome measure and other outcome measures may be presented at the discretion of the DSMB."

So the first order of business for you is to look at the data, the data quality, and in particular to satisfy yourself that the return rates and compliance with the protocol, the treatment, is taking place properly. It is one of your functions, isn't it?

A. Correct.

Q. If you go, please, to page 1397 the draftsmen or draftswoman of this charter has provided you with a form of words which is suggested you might like to use if you are satisfied with the data and you want the trial to continue?

A. That's correct.

Q. And the form of words include:

"we congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data."

That congratulation is a professional courtesy, isn't it?

A. It is a suggested wording and it is only to be included in the committee's report if the data merit that statement. It is not an essential part, this is just

a suggested wording.

Q. Now, in order to perform your safety function in the trial, the usual or default position is that you would receive cleaned data, ie data which had gone through a checking process; that's right, is it not?

A. That's correct.

Q. And there is no question, is there, that it would be appropriate to leave data unclean until the end of the trial? Data cleansing is a continuing process throughout the trial?

A. That's correct.

Q. And one of the purposes of continuing process is to ensure that the data monitoring board can perform its safety function, isn't it?

A. Yes, although the committee accepts that the data -- process of cleaning will inevitably never be complete until the end of the trial.

Q. There will always be outstanding queries of one sort or another?

A. Yes.

Q. But the data which is to be presented to you, as I say the default position is, data that has been more or less rigorously cleaned?

A. It depends how much time the trial co-ordinating centre has been given to prepare that data. There may be

circumstances when a data monitoring committee, having concerns about the safety of the participants, may request data rather more urgently, which may preclude detailed cleaning of the data.

Q. We will come on to that in a moment, Professor, if we may, but it follows from the default position that you are supposed to have clean data. That data cleaning must continue at a sufficient rate to allow you to consider at regular intervals, a~significant part of the trial population; that's right, is it not?

A. Correct.

Q. And one of the problems which is known to arise in clinical trials is that collecting and cleaning of data falls behind, with the result that you are not able to see a sizeable clean population of data. It is a well known problem with these trials, isn't it?

A. It can occur, but if the committee has limited data, its recruitment rate is going very fast, again it is a natural consequence that you just have to review the data that are in front of you.

Q. It is a serious problem, isn't it, if the data cleaning falls behind, lags recruitment, so that you are not able to see a significant population at any moment, with clean data.

A. It is a practical difficulty which the trial

co-ordinating centre has to deal with, but the decision making of the committee has to rest on the data that is presented to it.

Q. Can I show you a document in the rules and guidance file, please. These are two documents, one is a guideline on data monitoring committees produced by the Committee for Medicinal Products for Human Use?

MR JUSTICE BURTON: I am not sure I have this bundle. What is it called?

A. Rules and Guidance.

MR JUSTICE BURTON: I can see Charters and Agreements, Minutes and Reports, Standard Operating Procedures ... ah, Rules and Guidance, got it.

MR NASH: There are two sets of documents, in here, Professor. One is the rules and guidance produced by the Committee for Medicinal Products for Human Use. Is this a document you have had occasion to look at in the past?

A. Not this particular document. I'm familiar with a number of guidance documents on data monitoring committees and a number of published reports on their mode of operation, but not this particular one.

Q. If you go to page 9 within the same bundle, please, you will see a similar sort of document produced by the FDA. Is that one of the documents you have seen in the past?

A. No, but again, I have discussed this with colleagues, and I have read a detailed review of all of the documentation that has to be considered by data monitoring committees which were provided by Professor Adrian Grant for the National Health Service Health Technology Appraisal, called the Damocles Report, at which all these documents were reviewed, and I have considered that monograph in some detail.

So if I may just clarify, there are a variety of different guidance documents for people conducting data monitoring committees, and these were summarised and reviewed by Professor Adrian Grant in the report he provided for the National Health Service. And that provides a very health and systematic review for documents of this nature.

So I would like to say that although I haven't seen these particular documents I have actually read a review of all of these documents.

Q. Thank you.

If you go, please to page 32 within the bundle so, this one of the recommendations of the FDA document. Under the heading "Monitoring Study Conduct":

"The DMC [which is the equivalent terminology for a DSMB, of course] typically shares responsibility for assessment of data relating to study conduct with the

sponsor, the study leadership (such as a steering committee) and to some extent with IRBs. A DMC will generally review data related to the conduct of the study. That is, the quality of the study and its ultimate ability to address the scientific questions of interest in addition to data on effectiveness and safety outcomes."

Pausing there, do you accept that that is a fair description of the usual role of a DSMB?

A. The DSMB has to assure itself of the quality of the data, that is incontestable. Quite what data it does to do that is a matter for debate.

Q. And if you go, down, please --

A. I think it is fair to say that the data -- if you are a statistician or familiar with clinical trials, by looking at the data tables that are presented to you you can have a pretty reasonable idea about the quality of the data.

Q. Can you please look at the middle paragraph on the page, beginning:

"DMC ..."

"The DMC may issue recommendations to the sponsor regarding trial conduct when concerns arise that some aspects of trial conduct may threaten the safety of participants or the integrity of the study. For

example, if the data presented to the DMC are not current the DMC will not be able to meet its responsibility of ensuring that a study continues to be safe for its current and future participants. As another example, excessive dropouts may endanger the ultimate interpretability of the results."

That is making two points, there. Firstly, the DSMB has a responsibility to issue recommendations if there is a concern about the quality the data; do you agree with that?

A. That's correct.

Q. And secondly, one of the problems which would threaten the safety of participants in the trial is if the data cleansing process has lagged recruitment. So the data being presented is not reflective of the current trial population; do you agree with that.

A. Not necessarily.

Q. Why don't you "necessarily" agree with it?

A. Data cleansing generally removes rather trivial errors, that is, some typographical errors. It doesn't generally remove more major errors. The most important thing is for the data monitoring committee to review data on the largest possible number of subjects.

If, as happened in the BRAIN Trial, recruitment suddenly speeded up, we became aware that we would need

to review the data again fairly quickly when data on 100 subjects had accumulated, and the very nature of that request means that both data cleansing and data completeness will inevitably be not as good as they might have been had a longer period been allowed to elapse, and the data monitoring committee then had to balance considerations about the quality of the data it could, would look at, versus allowing more patients to be exposed to the drug. So the "perfect" must not be the enemy of the "possible". Going for perfection may not be the ideal in this circumstance.

Q. Now the transcript, I'm afraid, has missed one of your answers, Professor, but you said a moment ago that data cleansing generally removes trivial errors?

A. Relatively minor errors.

Q. Does it follow from that that it would be of concern to you if there was a large element of error arising, out of, for example, a misunderstanding of the trial criteria taking place at local level?

A. That would not be a source of bias.

MR BEAR: I wonder what issue this goes to.

MR NASH: The issue, my Lord, is described in the document, which I think was handed up to your Lordship, which is the data cleansing process being conducted by the School.

MR JUSTICE BURTON: Can you show me the paragraph?
MR BEAR: I'd also like to see a copy of that.
MR JUSTICE BURTON: Don't forget what you were going to say, we have got it recorded.
MR BEAR: We were only given one copy, I'm afraid.
MR JUSTICE BURTON: Yes, now which subparagraph are we on?
MR NASH: We are in subparagraph 2(b).
MR JUSTICE BURTON: Yes.
MR NASH: "There has been a failure to clean data properly or timeously, in particular: validate duplicate or incompletely reviewed ... failed to effect --"
MR JUSTICE BURTON: Sorry, my fault entirely 2 --
MR NASH: 2(b) on the first page.
MR JUSTICE BURTON: Yes, I have that, but there are lots of subparagraphs. Which one?
Oh, the general, 2(b):
"Failure to clean data properly or timeously, in particular ..."
Ah, I see.
MR NASH: Then we have a whole series.
MR JUSTICE BURTON: I have highlighted (b), which is our usual.
MR NASH: (a).
MR JUSTICE BURTON: I haven't highlighted (a), and we will come back to it, (c), which is whether non-fatal events

should properly be counted as SAE, which generally falls within, I think, our general question:

"Timing enquiries about information or clarification of AEs or SAEs; failing to review any report of any cause of death; timely reconciliation of data between different methods of SAE."

SAE, what is (e)?

"There were significant inaccuracies as between the data recorded on the database."

That again seems to fall within our general question. (f) is a general allegation of inadequate tracking of queries, (g) --

MR NASH: (g) is a timing point, my Lord.

MR JUSTICE BURTON: That is again, so, that is not the usual. (h) is not the usual, deaths probably falls within our usual case, and (j) certainly does.

So (a):

"LHSTM validated duplicate or incompletely reviewed entries ...

"(f) inadequate tracking of queries;

"(g) failure to effect a second data entry within five days of receipt.

"(h) failing to fully implement MedDRA coding."

Are those four allegations -- there may be more, I don't know, covered by your current pleading and/or

your present expert reports?

MR NASH: The pleading, my Lord, is expressed in general terms -- firstly, my Lord, the line of questioning I was just raising --

MR JUSTICE BURTON: Goes to --

MR NASH: Concerned particularly with (c), which is the:

"Failure to query in a timely manner the actual nature of coded events."

MR JUSTICE BURTON: I see, that is where that comes. We will adjourn any discussion of how far this case in its entirety is included for later, but Mr Bear wants to know to what issue does this questioning go? And you say this goes to 2(b) (c).

MR NASH: Yes.

MR JUSTICE BURTON: What do you say about that?

MR BEAR: The question I have from Mr Nash is whether there was a large element of error arising, for example, out of a misunderstanding of trial criteria, taking place at local level. The witness answered there would not be, but I can't see how that question, or any further questions can be developed, fit within (c), even assuming that (c) is something which has been properly raised, putting that to one side.

I thought we had actually covered -- I may be wrong about this, I thought in opening, to be put to Mr Nash,

and I stand to be corrected, that errors at local level weren't my client's responsibility and he agreed with that.

MR NASH: I am not talking about errors by clinicians at local level.

MR JUSTICE BURTON: What is this then? A large element of error arising out of a misunderstanding of trial criteria taking place at local level.

You are, I understand, not specifically honing in on that, but it is some sort of failure on the part of the defendant to appreciate that there had been a misunderstanding at local level, is that it?

MR NASH: Failing to query, as it says in the document:

"Failing to query, in a timely manner, the actual nature of the events."

MR JUSTICE BURTON: I can see that is a failure to query the actual nature of coded events, which, I've always understood -- up to now at any rate -- meant: are you sure this is an SAE, given that you didn't actually, or there doesn't appear to be, an SAE form. And so are you sure that what you have recorded in the CRF form is really an SAE, or has there been some reason for you not putting in an SAE form, or has there been some change of circumstances?

But that is my understanding. If that is it, then

that falls within the case as presently pleaded.

But if, however, it goes to some misunderstanding of the trial criteria, that doesn't seem to fall within.

MR NASH: We are not alleging that the School misunderstood the trial criteria, my Lord.

MR JUSTICE BURTON: Or that there was some misunderstanding of trial criteria at local level which the defendant failed to appreciate.

MR NASH: The case is that at local level there were SAEs that were being recorded as SAEs which either were not either SAEs at all, were simply not serious enough to constitute an SAE, or they were incidents which arose in the normal course of TBI. Whichever category those two events fell into, we say the School should have timeously queried the SAEs --

MR JUSTICE BURTON: I see that, but I don't see where it goes in terms of misunderstanding criteria. If a local man has called it an SAE but then not put in an SAE form, there could have been some query, or should have been some query at some stage, depending on whether it had to be done prior to being sent off to Professor Sandercock for 1st November, which would have reconciled the problem, and that might have shown there was some misunderstanding of the trial criteria. But what are you now -- it is much too general --

MR BEAR: Could I make an observation before Mr Nash replies? What he has just said is that at local level there were SAEs that were being recorded as SAEs which were not: either SAEs at all, not serious enough to constitute SAE, or they were incidents which arose in the normal course of TBI. To show that you would need to have a medical expert come along. Mrs Nickols disclaims any medical knowledge, and you would need to look at the case notes for the patients concerned. We would be a completely different legal trial. This is quite simply a new case, it is distraction from the issues, such as they be, that the claimant has chosen to put forward.

MR NASH: My Lord, I'm not how practically we can deal -- Professor Sandercock has very limited time with us.

MR JUSTICE BURTON: I would like you try, rather than asking him a general question, because it is pretty obvious if there has been a misunderstanding of the trial criteria at local level, ie they have made a complete bog-up, and there was something that the defendant should have done, earlier than it did it to find that out, I'm sure that witness is going to say: That is not the kind of trivial error that I was earlier talking about. But that doesn't help anybody. Can you try and articulate what it is you are saying in practical terms and put

that to Professor Sandercock.

MR NASH: Professor, you suggested a moment ago before that discussion, that what you would normally expect from data cleaning is the elimination of minor errors; correct?

A. To be completely clear, that is the sort of error that is most commonly dealt with. So, for example, it may be minor errors of transcription, and these are usually distributed in a random fashion between the treatment groups and make very little difference to the overall assessment of the effect of treatment between the different groups.

Occasional misattribution of events similarly has very little effect, overall, on the assessment of treatment effects. Therefore in this sort of circumstance, where the data monitoring committee wishes to see as soon as possible as much data as possible, it is a very common understanding amongst data monitoring committees that the data will necessarily be imperfect.

MR JUSTICE BURTON: I am going to put to you this allegation, Professor, I think it is probably the easiest thing to do, whether this allegation is properly within the trial is another matter.

The suggestion is that the defendant, before submitting the data to you, failed to query in a timely

manner the actual nature of coded events, including whether non-fatal events stated to be caused by TBI should properly be coded as SAEs under the protocol. Which is said to have led to the inclusion in the data presented to you of at least five patients in the shell table who had suffered at least at least one SAE who ought not to have been included. There is no indication whether those five patients were in any particular group.

Assume that was a failing about this particular defendant; (a) with what do you say about it, (b) did it have any impact on your job at all?

A. To answer the second question first, I think it is most unlikely to have had any effect on our decision making. Was it likely to be the case, yes, because some errors of attribution, causation, classification, occur in a trial and it takes time to resolve them, and the data monitoring committees I have worked on always understand that the complete resolution of suspected events may take quite a long time, even with the best endeavours. And therefore it is standard practice, it has been the practice on all the committees that I have served on, that one will look the unrefuted events. That is, events that are suspected but not yet fully confirmed to be or not to be events, because that, if you like, gives

the best estimate of whether there is likely to be a problem or not.

MR NASH: Let me move on to the data management plan, Professor, and you will find that in the second core bundle.

A. Sorry, could you repeat that?

Q. The second core bundle, I think it is to be handed to you, at tab 16.

I would like to ask you, please, to turn to page 283, which deals with the soft lock procedure as operated for the purposes of this trial:

"The soft lock is to take place six weeks before a DSMB meeting to ensure complete patient data is presented ..."

Soft locked operated at patient level, that is, only patients with complete data will be considered for soft lock.

And then some instructions are given to the data manager as to how the soft lock is to be operated -- I'm sorry, are you struggling with the papers?

A. No, I'm just getting some of my own papers.

Q. The data manager is given some instructions.

"The data manager must make sure the following task is completed before the soft lock is done. First and second entries have been, comparison has been done for

all selected patients, all queries have been resolved for the selected patients, or only insignificant data queries forms are outstanding, and all SAEs for the selected patients have been reconciled."

Did you understand that that was how the soft lock was operating in this trial?

A. I have to be honest, my Lord, I cannot recall seeing this particular document. We were aware that is soft lock would need to be performed if the trial was going smoothly and as anticipated. However, the trial wasn't going as anticipated, because at our first meeting on 13th September we already had some concerns which I will not go into in great detail, but we did have some concerns, and therefore our overriding concern was not with soft locks and minor degrees of tidying up the data. We wanted to see the next batch of data as soon as it could be assembled, which would preclude a soft lock.

Q. I am going to come on to this meeting, Professor, and this is not --

MR JUSTICE BURTON: Talking of having limited time, shall we take the short break for the shorthand writer now, and lets just indicate what time we are going to sit until. 5 o'clock, 5.15, when are you going to finish?

MR NASH: I think 5 o'clock is probably sufficient, my Lord.

MR JUSTICE BURTON: We will come back before 3.45 and go on until 5 o'clock.

(3.40 pm)

(A short break)

(3.45 pm)

MR JUSTICE BURTON: Yes.

MR NASH: My Lord, looking at the soft lock, Professor, it is clear that the purpose of the soft lock is as explained here, to isolate a population for whom clean data is going to be presented to the DSMB; correct, isn't it?

A. As I explained, the purpose of the soft lock is all very well if the trial is going smoothly and there is no apparent hazard to the participants in the trial.

Q. I will come on to the exceptions, Professor, but as set up --

A. It is a perfectly reasonable procedure, yes.

Q. And as established, it was meant to happen six weeks ahead of the DSMB meeting, wasn't it?

A. That is my understanding.

Q. And it follows, doesn't it, from that, that it is expected that the data cleaning process is running at a sufficient rate as against recruitment, so that the locked population will represent a useful sample for the

DSMB meeting, six weeks ahead of the lock being applied?

A. Yes.

Q. And if there is a discrepancy between the locked group and the total population when the DSMB meeting takes place, that is a serious issue of safety?

A. It is not.

Q. Perhaps I could just finish the question, Professor?

A. It isn't, I'm sorry.

Q. Can I just finish the question --

MR JUSTICE BURTON: Just finish the point and then ask your question.

What is the point you want to make?

A. The point is that a discrepancy of a few events is not very material in the decision making that this sort of data monitoring committee makes. But I'm sorry to interrupt.

MR JUSTICE BURTON: Now ask your question.

MR NASH: Professor, the question was not concerned with the number of events or discrepancies within the event, it was concerned, please, with the discrepancy between the isolated population for the lock and the total population for the trial, and if there is a large discrepancy between the two, I am suggesting to you that that is a serious issue which would give rise to concern.

A. Why is that?
Q. If you have a trial population of 150 and when you arrive at your DSMB meeting you are only given 10 patients within the soft lock, your reaction --
A. But, okay, as trialists, we are all familiar with the rate at which data will accumulate at different stages of a trial. The first analysis, when we looked at the 13th September, at about 40 patients, I don't have the exact numbers in front of me, was that at a very early stage, for to us look at the shell tables, did they look sensible, were the accumulating data looking appropriate to the sort of patients going into the trial, and that was indeed the case.

But to our surprise we saw the trends were not looking favourable.

So, as experienced managers of trials, all of us three, we realised that the flow of data was inevitably going to be imperfect. So I fail to see the relevance of this line of questioning. We knew that we would have an incomplete set of data, that wouldn't -- the only -- can I just point out --

MR JUSTICE BURTON: Just answer, yes.
A. Can I just point out, if we have the totality of the data here, which we perhaps represent as a large circle, and within it is the smaller circle which you refer to

as the locked population. If we look at the distribution of events within the larger group or within the smaller group, they will be approximately similar between the treatment groups. Therefore the only difference, in reality, to the decision-making process is that if we look at the smaller locked group, we will have slightly wider confidence intervals than if we look at the whole population. But they are broadly speaking going to produce similar estimates of the effects of treatment.

MR JUSTICE BURTON: Does your proposition, Mr Nash, depend on the difference between 10 and 150, which is rather a dramatic difference? Or -- I don't know whether Professor Sandercock agrees that that makes a big difference.

What was being put to you was: if you have a locked population of 10 and a broader population of 150~--

A. Well, that clearly is a very big discrepancy, but that is not the sort of discrepancy we were looking at. We were looking at the sort of discrepancy that we would expect, given the rate of recruitment.

MR NASH: I was simply seeking to establish with you that a discrepancy between the locked population and the total trial population could raise issues of serious concern because it would suggest that data cleaning was falling

behind recruitment?

A. It could, but it didn't.

Q. Lets look at what actually happened at the meeting of 13th September. We have the minutes for that meeting at tab 20 of core bundle 2.

A. Sorry --

Q. Core bundle 2, tab 20?

A. I have that, 13th September.

Q. 13th September, yes. These minutes, I think, were prepared by Mrs Shakur, and approved by the board, the DSMB; that's right, isn't it?

A. That's correct, yes.

Q. On the first page we see the recruitment rate, and it is clear from that that within the last, I think, probably two, possibly three months preceding the meeting recruitment had increased rapidly, particularly in August, yes?

A. Yes.

Q. And if you go over the page to 2182, under the heading "Data quality":

"HS [Mrs Shakur] explained that although 122 patients were randomised at the point of the DSMB, only 66 patients had baseline data entered and 42 had complete data which were presented in the DSMB report."

Now, that is telling us three things, isn't

it: firstly, the locked population is 42, out of 122; correct?

A. Yes.

Q. 66 patients have only the data which has been entered when they begin the trial?

A. Yes.

Q. Baseline data. And the balance, which is 24, who are randomised within the trial, have no data at all; that's right, is it not?

A. There is nothing unusual in that.

Q. Well, I'm suggesting to you, Professor --

MR JUSTICE BURTON: It is 14, isn't it, rather than 24?

MR NASH: Have I done the maths wrong?

A. Can I just point out that that is an inevitable consequence of the design of any randomised trial, that you get the baseline data first, and you will always have more of that. I don't see the problem.

Q. I am sorry, Professor, 14. I misled you on the numbers, 14 have no data at all?

A. That is trivial, when you are planning to recruit several hundred, and you are at an early stage of the trial, that difference is completely immaterial.

Can I just ask, can have you been involved in a clinical trial yourself?

MR JUSTICE BURTON: I don't think you can ask counsel

questions.

MR NASH: I am sorry, Professor, that you are finding these questions irritating.

A. I am sorry to get irritated, I to do apologise.

Q. I am sure we will --

MR JUSTICE BURTON: What you can safely say is that you can assume that Mr Nash is putting these questions on instructions.

A. Yes, yes.

MR JUSTICE BURTON: And therefore you can criticise if you want to, whether it helps anyone -- it is the nature of the instructions.

A. I do apologise.

MR JUSTICE BURTON: Mr Nash, the person who instructs you, can't understand clinical trials. That is a fair enough comment.

MR NASH: I suggest to you, Professor Sandercock, when you are presented with a trial which has a population of 122, where you are going told that only 42 have complete data for you to consider for safety purposes, that is a matter of concern, an issue which would cause to you consider whether the data cleansing process had fallen behind recruitment; is that right?

A. I think, in the way that the data were presented to us by Mrs Shakur and knowing the context in which the trial

was being conducted, in places like Colombia, and in the environment, we felt that the rate of data completion was entirely satisfactory.

We discussed the provenance of the data, the completeness of the data, and the data as it looked in the tables and, as we said in our letter, we had no concerns.

MR JUSTICE BURTON: Well, this one we are looking at is 13th September, the earlier one --

A. Not about the quality of the data.

MR JUSTICE BURTON: Hold on, lets set this in context. At 13th September you saw this, and then you formed a view as to what you would like to see next time.

A. Yes.

MR JUSTICE BURTON: What you are being asked about at the moment is when you formed a view as to what you would like to see next time, did it concern you, and if so, why/why not, that you had only 42 patients with complete data?

A. Did it concern us? No, we just wanted to see the data again fairly quickly when the data had been processed, and we set a time when we estimated that we would have data on approximately twice as many patients, and we set upon the date of 1st November.

MR NASH: We see that at the bottom of the page:

"Reconvened with a target date of 22nd October 2007."

And I suggest to you that the reason why you fixed that target date so quickly was because you were concerned, at this stage, that the data cleansing had lagged recruitment.

A. No, we were concerned about the effects of safety. I am not quite sure what I'm at liberty to reveal --

MR JUSTICE BURTON: You are at liberty to reveal anything because we are in camera.

A. In the first interim analysis, then, the trends were not looking favourable across the various domains we have talked about at length already, and therefore, not because of concerns about the quality of the data but for the safety of the participants in the trial, which was our overriding concern, we made the request that we did.

MR NASH: Now, you suggest in your witness statement that there was a specific decision that the soft lock procedure should be removed for the next meeting, and that that was communicated to Professor Roberts and Mrs Shakur. Can I just remind you what you said about that.

Paragraphs 44 and 45 of your witness statement. We can pick it up perhaps, at the bottom of page 15 of the

document:

"The members of the DSMB considered that the application of soft lock some weeks before the analysis was neither practicable nor desirable and was considerably less important than having information on the largest number of subject patients in the full knowledge that the data we would be reviewing had not been cleaned. This point was discussed between the DSMB and Professor Roberts and Haleema Shakur at the end of the teleconference at the end of 13th September 2007."

Your evidence, I think, when you were answering questions from Mr Bear, did not suggest that there had actually been a discussion of the soft lock with Mrs Shakur and Professor Roberts; can you recall now whether that statement is correct?

A. I have to be perfectly honest and I cannot remember the exact form of words that I used. I will be completely honest with you. What we made clear, whether or not we specifically mentioned the soft lock, was that we wanted the data, irrespective of whether it had been cleaned or not.

Now, to my mind that is an implicit statement that the procedure of soft lock could not be applied because we wanted to see as much data as possible, whether or not it had been cleaned.

So I have to confess that I cannot remember the precise words of the discussion that we had, but the request, and the instruction, and I believe, without having the statement in front of me, but the actual point that Mrs Shakur made would have precluded that, would it not, pretty much? Because looking at the recruitment that was occurring, it would have been impossible to do the clean-up in time.

MR JUSTICE BURTON: There were six weeks between the 13th September and the next week.

A. Thank you for pointing that out, my Lord, sorry, which completely precludes it, so it was kind of self-evident to us that that was going to be the case.

MR NASH: Well let's just see what is self-evident. You are right, it was a six week period, so the soft lock could not operate unless it operated on that date to isolate the clean population which of course you had already seen.

The purpose of the soft lock is simply to isolate, six weeks ahead, the population which is going to be presented to the DSMB; correct?

A. Well, it is a procedure that you can do that does impact to some extent on the completeness of the data set.

Q. Professor, we looked a moment ago as to the provisions as to soft lock, and they are very clear, aren't they?

The trial manager isolates the relevant population six weeks ahead and says: these people are going to be clean for the DSMB. That, is how it works, isn't it?

A. If the trial is proceeding in the fashion that is not giving rise to safety concerns.

Q. And it follows from that, by saying simply don't worry about the soft lock, don't apply the soft lock, you are not suggesting to Mrs Shakur or Professor Roberts that you expected to receive unclean data, are you?

A. We would expect them, as any trial management group would do, to make their best efforts to get the data as clean as possible. That is what every trial office does in preparation for every data monitoring committee. You do the best that you can.

Q. So whether you are fixing the new date, if possible in the week beginning 22nd October, you are expecting, of course, the cleaning process to continue from the day of 13th September onwards; correct?

A. The patients -- yes, for the patient coming into the trial, that's correct.

Q. What you are hoping to achieve is that on 22nd October you will receive clean data for 100 patients?

A. Or however many patients -- if it happens --

MR JUSTICE BURTON: Just so I can be clear about this, Mr Nash, until we have the long-heralded

cross-examination material as against Mrs Shakur, the only lack of cleaning I know of is the failure to reconcile the CRF with the SAEs which of course you have asked questions about, and you can no doubt come back and ask some more if you wish, but if is there some other lack of cleaning, or lack of best endeavours to be as clean as possible that we have in this case?

MR NASH: Yes, my Lord, it is the document we were looking at a moment ago, the pleading document that was handed up some time ago.

MR JUSTICE BURTON: Well, given that Professor Sandercock is here, you ought to -- I'm not sure it helps to have these general questions about cleaning. It is obvious that, well, we got it from Professor Sandercock now, so I can say it is obvious, it is obvious to me at any rate, it is obvious to him, that the defendants would not take: get the stuff to us as much as you can, as soon as soon as possible, as a licence to produce complete rubbish. They will want to use their best endeavours but they will not have to comply with the soft lock.

Then the question arises as to whether they have to reconcile the SAEs with the CRFs, and we have got that as a separate issue.

But if there is something else they failed to do

then I think it ought to be put to Professor Sandercock as to whether he would have thought that they should have at least done that, whatever it is they didn't do. Now what is it that screams out of here:

"Validated duplicate or incompletely reviewed entries ..."

I don't know what that means, but that is (a).

(f):

"Inadequate tracking of queries ..."

I don't know what means. (g) is new to me about failing to effect second data entries, and certainly completely new to me is MedDRA coding.

If those are issues in the case, at all, I think that is the kind of question I would find valuable to put to Professor Sandercock, as to whether, not only by sanctioning, indeed requesting the lifting of the soft lock and given the timescale between then and the next meeting, just produce the best you can, would that include or result in these other alleged failings, whatever they are.

MR NASH: My Lord, Professor Sandercock in his statement has said on a number of occasions that the normal error in unclean data is not something of concern.

MR JUSTICE BURTON: No, but I don't know whether MedDRA coding not being fully implemented is or is not

1 something of concern, assuming that it happened.
2 A. Well, I can deal with MedDRA very shortly, but the
3 before I get to that, the suggestion from
4 Professor Sandercock has been that, having had the
5 meeting on 13th September, they fully expected on
6 1st November to receive unclean data, and that wasn't --
7 MR JUSTICE BURTON: Yes, reasonable best endeavours to be as
8 clean as possible, is what he says.
9 MR NASH: I am exploring now exactly how far that goes.
10 MR JUSTICE BURTON: Do bear in mind the specific
11 allegations, if indeed you are permitted to make them.
12 MR BEAR: As far as the MedDRA is concerned, maybe I have
13 missed something, that there is a reference to HW
14 supplemental 8. HW I assume is Heather Wells, were we
15 aware of a second supplemental report from Mrs Wells?
16 MR JUSTICE BURTON: Where is that, where is this?
17 MR BEAR: It is in H, but I have been told that we do have
18 it. No.
19 MR JUSTICE BURTON: In my H, I haven't got it, I wonder if
20 I have a different H to me.
21 MR BEAR: This is the MedDRA one.
22 MR JUSTICE BURTON: Yes.
23 MR BEAR: If you look it the bold at the end. Perhaps you
24 don't have it.
25 MR JUSTICE BURTON: My (h) says:

"In breach of protocol and DMP, failed to fully implement [splitting the infinitive] MedDRA coding. As a result they were not able to send all the requested shell tables to the DSMB."

MR BEAR: Mine goes on to say "HW." And then it gives a reference, that must be Ms Wells, "HW supplemental", and it gives another reference, and then it says "HW second supplemental" and I'm not sure we have seen a second supplemental.

MR JUSTICE BURTON: I don't have any of that in the piece of paper I was handed yesterday. You were given that today, don't worry about it.

MR NASH: I think the version Mr Bear has includes the reference for pleadings and so forth that your Lordship asked to be put into that document.

MR BEAR: But my concern is that it refers to a document which I am not sure we have ever seen.

MR JUSTICE BURTON: No I understand what you are saying.

MR BEAR: Is there a second supplemental report and we haven't seen it?

MR NASH: You haven't seen it.

MR BEAR: We haven't seen it. So you are referring to a document that we haven't been given. What a joke.

MR NASH: My Lord, we will leave the MedDRA coding to one side for a moment.

Can I please complete my cross-examination of Professor Sandercock?

MR JUSTICE BURTON: It is simply that we won't have him back again. So if you are going permitted to run these three or four extra points, if they are extra, I think they ought to be put to Professor Sandercock, albeit he will not be prepared for them by having not seen the supplemental report of Mrs Wells. Anywhere, there it is. Yes.

MR NASH: Professor, we will continue on the course I was on, concerned with the decision of 13th September, and I think you have suggested, you have accepted that whatever was or was not said about the soft lock, when you wanted to see a population of 100 by 22nd October, you wanted to have that as clean as possible, that information.

A. That is correct.

Q. And I am suggesting to you that you would have expected that to be substantially clean?

A. Not necessarily. We just ask that it be as clean as possible. In the time available, you know, communicating with remote parts of the world, you know, these things don't happen quickly.

Could I also point out that in scheduling data monitoring committees meetings, the first meeting, when

you have real data, is usually -- how can I put this, a very sort of straightforward affair and it goes quietly and you say, okay we will meet again in six months time or something like that. This was a very different sort of meeting, and I think we were sufficiently alarmed by the accumulating data, it is very difficult to convey this, but our concern is for the patients' safety, and the data in front of us suggested there was a problem.

Q. Can I just ask you about data and data error. You refer in your statement several times to what you call the play of chance. That is a reference to all of the uncontrolled variables that may affect the outcome of a trial, is that right?

A. When you observe the effects of treatment, let us say the number of deaths between treatment and control, the number of events will be determined partly by the randomness, the stochastic nature of events, part of it might be determined by bias, and it is the combination of those two, the sum of those two, that leads to the observed effect.

Q. What may happen, simply, is that more people die in the treatment group than the placebo group because it happens at any particular moment that they are randomised into the treatment group with more serious

injuries or are simply constitutionally weaker. That would be one illustration of the play of chance affecting results, would it not?

A. Well, that would be -- that is partly a result of bias, because your randomisation procedure has not resulted in equal distribution of severity across the treatment groups. That is a feature of poor design, and in the BRAIN Trial the baseline characteristics were balanced. So that had not occurred in the BRAIN Trial. They designed the trial appropriately to minimise that form of bias.

MR JUSTICE BURTON: Who is "they"?

A. The investigators, the London School of Hygiene --

MR JUSTICE BURTON: Part of their task was to randomise, not only to anonymise, but also to randomise people with different severity of symptoms.

A. And to ensure that the design of the system that allocated the treatments ensured that the factors that might most importantly determine outcomes, such as the severity of the injury, would be evenly balanced between the groups, so that any observed differences in the frequency of death would be more likely to be due to the effects of treatment than some bias by the use of a poor design.

MR NASH: Another element where the play of chance can come

into effecting the results are mistakes made by the people gathering the data, isn't it?

A. What sort of mistakes?

Q. Simple mistakes of omission, failing to fill in a form or failing to tick a box, or mistakes about the trial criteria, as well, can't they?

A. It is recognised that minor inaccuracies in the categorisation of the type or severity of a patient's disease, does not have a material influence on the assessment of the effect of treatment.

Q. The goal is consistency of the data across the sample population, consistency by eliminating errors of that kind, isn't it?

A. There is a need to eliminate errors, but there is also a need to eliminate bias, and ensuring that there is strict randomisation, and that there is no foreknowledge of the next treatment allocation and ensuring blinding of the assessment at the outcome are probably far more important.

Q. You minimise the effect of the play of chance generally by increasing the size of the sample population?

A. Indeed. If you are assessing the effects of treatment in looking for benefit, such that you might then go out and market the drug, but at this stage of the drug's evaluation there was insufficient prior knowledge of its

effects.

Q. Paragraph 16 through 18 of your statement, you suggest that haphazard errors are of no concern because they could be expected to be distributed evenly across the treatment the placebo groups; do you remember say that?

A. Yes, I do.

Q. Doesn't the probability of that depend upon the size of the population you are looking at?

A. Frequency of errors will depend on all sorts of things. It is not dependent on the size of the population that you study.

Q. No, I think you understand that that is not what quite what I was asking, I was asking about the distribution of errors across the groups?

A. I am not sure I understand why the distribution of errors should alter with the increasing number of patients in the study.

Q. You suggest that the probability is that they will be distributed evenly across the groups?

A. Yes.

Q. I am suggesting you that whether or not that is probable depends on the size of the population?

A. If we say that there is -- an error will occur in about 1 per cent of the patients included in the study, then it is immaterial. That percentage will not alter the

more patients you include in the study. The 1 per cent error will apply across all the treatment groups, provided there is not a 5 per cent error in the treatment group and 1 per cent error in the placebo group, you will be fine.

Q. If you look at what you say in paragraph 14 of your statement:

"Where the number of patients relatively small and hence the numbers of events would be small, as it was in the BRAIN Trial, the potentially very large effects of the play of chance mean it is of paramount importance to preserve blinding ..."

The point you are make something that the size of the population affects the play of chance?

A. This is a different point. This is a different point, and it is alluded to in the book by Ellenberg, that if the sponsor becomes aware of a trend in one direction or the other, based on a very small number of patients they may inappropriately reach decisions about the stopping or the continuing of the trial. The data monitoring committee will be well aware of this. It is therefore to avoid inappropriate decision making that the blinding has to be preserved.

Q. If we are concerned, Professor, for example with a small number of patients and the AE count in each group:

a small number of patients with a number of AEs that are higher than the mean, if they are located in a particular treatment group by chance, that could exaggerate the apparent trend, couldn't it?

A. If the events were low in frequency. But actually the most striking unevenness of distribution was not in deaths but in serious adverse events, so that was the most statistically robust finding of an uneven distribution of bad things happening in the treatment groups, so I don't quite get your logic.

Q. Does it follow from that that you agree with my proposition that if you have a small population and you have a small number within that population with a higher than average number of AEs, and they happen by chance to be in one group rather than another --

A. But the statistical analysis suggests that the play of chance was rather unlikely to explain this particular result.

Q. By the same token, if a number of patients had AEs lower than the trend and they happened to be located in the placebo group, that too would tend to exaggerate the apparent harmful trend?

A. Well, but I have just said that of all the results that we looked at, the most significant, that is the one result in which the play of chance was least likely to

be operating, was the effect on the serious adverse events. I could accept your argument if we were talking about the deaths, where the difference was not statistically significant, but I fail to see it in relation to the serious adverse events where there was a three-fold difference which was extremely unlikely to have arisen as a result of the play of chance.

However, as a data monitoring committee we were aware of the fact that the play of chance can sometimes, in these circumstances with small number of events, be extreme, and that is why the preservation of the blinding was essential, at least until we had seen the next analysis, when we had 100 patients in.

Q. Can I suggest this to you, Professor: if you have a mix of data, some of which has been cleaned, and some of which has not, that is going to introduce a further element of chance into the analysis, isn't it?

A. It gives you a smaller sample and therefore you may have less precise estimates.

Q. I am not talking about isolating a sample, Professor, I am talking about being presented with a mix of data, some of which is cleaned and some of which is not?

A. It doesn't introduce a bias between the treatment groups, which is what you are trying avoid above all else.

Q. If it happens that the cleaning process has the effect generally of eliminating SAEs, and if it happens that the placebo group has been more thoroughly cleaned than the treatment group, that might lead to a false conclusion, mightn't it?
A. That is a very unlikely sequence of events, since the cleaning process is done blinded to the treatment allocation. Such an occurrence would depend on the person doing the cleaning having the prior hypothesis that an SAE was less likely to occur in the placebo, which is precisely why the cleaning process is done blind.
Q. Again, it could work the other way. By chance the cleaning process has been more extensive in the treatment group than the placebo group, that might also disguise a harmful trend?
A. Yes.
Q. And the possibility that this might occur is increased in a small population; do you agree with that?
A. Well, in the process of data cleaning, which is cleaning out things that -- it is -- in the process of designing and running this trial, all of the systems were designed to minimise the risk of bias in the assessment between the different treatment groups. Everything that you do in a trial seeks to minimise bias. That is, you do more

of one thing in one group than another.

Q. Can we agree, please, that the population for the meeting on 1st November, only 140 patients in the data set, is a very small population for assessing safety and efficacy?

A. It is, but as a data and safety monitoring committee our terms of reference very clearly stated that because we were looking at safety we could not predict which aspect of the data that would be presented to us should take precedence, and therefore we would have to use our best clinical and statistical judgment in forming a view on the basis of all of the evidence that was presented to us, and therefore that was -- that was the founding basis on which we made our decision. Not particularly on the SAEs, not particularly on the Hireos, not particularly on the death. It was on the pattern of all the information that was available to us, for the very reasons you have just been cross questioning me, because of the concern about the play of chance.

MR JUSTICE BURTON: You were aware, you have said, on 1st November, that the data that you were being provided with might well be unclean, you were entitled to assume that reasonable endeavours had been used by the defendants, given the short timescale, but you knew, nevertheless, that the data could be unclean.

A. We did.

MR JUSTICE BURTON: Did you make any allowance in the conclusion that you reached in (a) of your conclusion -- never mind (b) -- in considering the SAE position, did you make any allowance for the play of chance, the probability that there might be errors and that those might have been unevenly distributed by pure chance between the different groups?

A. We did, and we took particular heed of the advice from Professor Steven Sen, who was the expert statistician of our committee, who took the view, and I have to bow to his statistical judgment, that, firstly, the play of chance was unlikely to be an explanation for this observation, and secondly, that even were more data to accumulate that it would be very unlikely for this trend to be reversed.

Like Professor Roberts we were very keen that this treatment be proven to be beneficial, because there aren't many treatments that are effective in this particular population. So we had the starting point that we hoped, like Xytis, that this treatment would be effective. However, our observations, our discussions, which were prolonged, formed the view that as things stood on the 1st November the play of chance, the lack of data cleaning, were unlikely explanations for the --

for the observed pattern of adverse events and therefore our conclusion was that bias, due to poor trial design, the play of chance, due to small numbers, were not the explanation, and that the explanation was that this was an effect of the treatment, and that the only way of resolving whether or not that was the case was to suspend recruitment, examine the data that was accumulating in the patients already randomised as quickly as possible, and then a decision, based on larger numbers of patients, could be made as to whether the trial could be restarted in the hope that with the accumulation of more data, the trial would in fact show a benefit.

MR JUSTICE BURTON: Mr Nash?

MR NASH: We will come on to the meeting now, Professor.

It is not, I think, clear from the papers exactly whether you received the shell tables from Sealed Envelope, but it looked as if it was round about 26th October. Can you recall now whether that seems about right?

A. I'm afraid I can't recall exactly when I received the papers. My schedule is that we have a data monitoring committee, I have to review the data in detail and be thoroughly prepared. My responsibilities as chairman are very onerous and therefore I have to prepare in some

detail. So I normally would spend at least a day or two going through the numbers very carefully, and in this particular occasion, when we were so concerned about the safe the participants and it was clear we were going to face quite a difficult decision, I actually spent quite a long time -- I can't remember, I would have to look at my calendar to see what the date of the 1st~November was, but if it was early in the week I would probably have spent a day or two over the prior weekend going through the numbers. But I can't recall, I'm afraid, without looking at my diary, which isn't here.

Q. Bear with me for one moment.

Can you take up chronological bundle 10, please. Page 2774. Perhaps begin at 2773. This is a more complete version of the second interim analysis than I think we have in the core bundle, and if you go, please, to page 2774, the introduction. There is no indication there, in that introduction, of the extent to which the cleaning process had been completed in relation to this data, is there?

A. No.

Q. Do does it follow from that prior to the telephone meeting on 1st November, you had no means of knowing, or no indication from Sealed Envelope, how much of the data was clean and how much was unclean?

A. Correct, but one has some estimate from it from the number of missing variables or things that look inconsistent in the data, to get a general picture of the quality of the data.

Q. When you say you have some idea of it, you mean you have some idea of the clean population as against the unclean population?

A. No, you have an idea of the general quality of the data. If the date, the variables, are buy and large complete, the numbers all add up, then you can be reasonably trusting of the data, and this data set appeared to us to be of high quality.

Q. You told us a moment ago that you spent a day or perhaps sometimes two days looking at this material; does it follow from that that you had formed a provisional view before you had the telephone meeting?

A. I found the statistical analyses quite complex and I was therefore very interested to see how Professor Sen interpreted the various statistical tests of the various different key variables that we were looking at in table 5 and table 7, as to what his interpretation of the play of chance might be.

Q. Had you formed a view before the telephone conference that recruitment should be stopped?

A. Well, I think we formed the view that -- when we had our

first meeting, that we might be calling for a stop in recruitment at our second meeting. That -- from the trends that emerged in the first interim analysis, we already had some thought that that might be the case.

Q. Can we turn up, please, the minutes of the meeting which are in the second core bundle at tab 21.

Again, prepared by Haleema Shakur, and recording the events of the first open session?

A. Sorry, are we referring to page 2748?

Q. Yes, in tab 21?

A. Yes.

Q. First open session:

"Haleema presented an update on recruitment and data quality. It was noted 225 patients recruited to date. It was pointed out that in the interests of patient safety the DSMB had been given all of the trial data up to the date of the DSMB data download ..."

Which we know is 19th October:

"... and that the data on the more recently included patients had therefore not been completely cleaned."

Now, Haleema Shakur, having made that statement, did you test her on the extent of cleaning within the population that had been presented?

A. No.

Q. Did you seek to find out from her how much of the

population was clean and how much was dirty?

A. Well, to our -- for our deliberations that was less important than having an estimate, which we were given by the consort flow chart at the first page of our second interim analysis, which outlined the number of patients for whom data were, as yet, unavailable.

Q. I am not at the moment focussing on the conclusions you made, I am asking --

A. What I am trying to convey is, when a data monitoring committee asks -- as you have asked me already and I have given my permission on this -- you make an opinion about the quality of the data, but the other thing that you need to know about is: how much data will be available? You know that you have some data, be it of an uncertain quality, that is presented to you in the tabulations, and you know that there will be more data to come. And it is trying to estimate how much that data that is, as it were, on its way into the database, might influence your decision making.

That, in our mind, was the more important piece of information.

Q. We looked a little time ago at the duties which the DSMB undertook in relation to this trial, and one of those was to monitor data quality; do you remember that?

A. Yes.

Q. And I think you agreed with me that that was an important safety consideration for the conduct of a trial, the FDA guidance in relation to that, do you remember that?
A. That's correct.
Q. You are now being presented with a mass of data which you are being told has not been completely cleaned. I would like to know why you didn't think it appropriate to test that statement by finding out more about the processes which were being gone through?
A. Well, could I point out that the BRAIN Trial is no different to just about every other trial, be it run by a pharmaceutical company or be it run by an independent group of prestigious investigators, that inevitably, at the time the analyses are presented to the data monitoring committee, the process of data collection will be incomplete, to a greater or lesser extent. And the fact that in the BRAIN Trial the data was to some extent not complete was not exceptional, and therefore your suggestion that the data were of an exceptionally poor quality, or that we were being given data that was exceptionally incomplete, you know, it is not appropriate.
Q. No, on the contrary, Professor, you are being told something which suggested that the data was more or less

complete, weren't you?

A. No, we were aware --

Q. You don't read that statement to that effect, if you look at 2478:

"The data on the more recently included patients had therefore not been completely cleaned."

That is implying that this is a minor lagging in the cleaning process, isn't it?

A. No, it just says that it has not been completely cleaned, and -- to repeat what I have said, to us, the more important thing was to get an estimate of how many deaths, how many serious adverse events there might be in the patients randomised but yet without CRFs reporting 15 day outcome on the database. That to us was the more important consideration, but the amount of data that was due, or the lack of cleaning, was not exceptional.

You see, by the time of the.

Q. The population in the trial had increased again very rapidly, 225 statement; that is right, is it not --

A. That's correct.

Q. -- on 13th September. So if, in fact the position was, for example, that the clean population had only increased from 42 to 50, you are falling even further behind than had been the position in September; correct?

A. Yes, but we were given data on 100 patients.
Q. But you didn't know how much of that data was clean, did you?
A. No.
Q. And you didn't make an inquiry of Mrs Shakur, when she makes her statement that some of the data is not completely cleaned, you didn't make an inquiry of her to find out?
A. We did not.
Q. Would that not have been an appropriate inquiry to make?
A. The data monitoring committee made a judgment call as to whether to pursue that line of questioning or to consider the more weighty matters of the data that we had in front of us.
Q. Was that a judgment call that you discussed amongst yourselves?
A. Yes, of course it would be. But not in the open session.
Q. Your evidence is that you decided that you were not going to test Mrs Shakur on the extent of the cleansing of the data, is that right?
A. The discussion in the data monitoring committee took account of Mrs Shakur's statement that the data were not completely clean, without further specification of the extent to which it was not completely clean.

Our deliberations focused on the data in front of us, and that is what our discussion focused on.

MR JUSTICE BURTON: But for the intervention of the alleged termination of the contract of the CTSA by the defendants, which took place in the next couple of days in the first instance, and then continued with various notices thereafter, can you give me any indication in the relation to the answer you gave, it is at page 92, just a few moments ago, when you said that your conclusion was that the only way of resolving whether or not that was the case, that is your provisional conclusion which led you to suspend the recruitment, was to suspend recruitment, examine the data that was accumulating in the patients already randomised as quickly as possible and then make a decision in the hope that with the accumulation of more data, that the trial would in fact show a benefit.

I know it is hypothetical, because it didn't happen, but what sort of timescale are we talking about? Assume there is no intervention by Xytis at all and after your 1st~November suspension of recruitment this now takes place, would have taken place, suspend recruitment, examine the data that was accumulating and being randomising and make a decision; presumably you would have another DSMB meeting to look at the fuller

information. What period of time are we talking about?

A. The team are pretty effective and have very good communication, so we could probably give them a target of:

"Can we meet again in a month or two with as much as you have got by then?"

I would expect a pretty reasonable proportion of the 225 to be available then. One is only asking for outcome data after 15 days of randomisation and that could be got in pretty quickly. So, you know, I would expect within a month or two one would probably have had a substantial proportion.

However, that is a opinion, and what would normally happen for the data monitoring committee is, they will say to the trial managing the team: how quickly can you get this stuff in so we can look at it again? So I am just estimating a month or two to get another worthwhile chunk of data to look at on the 225. It is only an estimate.

MR NASH: Now, knowing as you did on 1st November that the data was not clean, and indeed that this was something you had anticipated would be the case, would you not think it appropriate -- didn't you think it appropriate to call for sight of the statistics from the HPM database, to compare with the data you were being given?

A. That might well have been the case, in the process of resolving -- yes, I mean of course that would happen, because once you have stopped randomising, what then happens is you try and resolve everything --

MR JUSTICE BURTON: You stop recruiting?

A. Stop recruiting. You then try and resolve everything. So, in the process of cleaning up the data of course you are going to have to reconcile those two databases, but because they operate in different ways for different purposes you can't reconcile the two until all patients have stopped being followed up and no new ones have been recruited and you have worked through the process of trying to figure out whether these were adverse events or not, and HPM has done its work of assessing each individual event.

So the two -- you won't -- sorry, that is all I want to say.

MR BEAR: Can I remind my learned friend that in paragraph 25 of his skeleton he said:

"Finally, it is emphasised that Xytis do not criticise the decision of the DSMB to recommend suspension of the trial on the basis of the materials which were presented to it. It was the right decision."

Is he now departing from that?

MR NASH: No, my Lord, it is perfectly clear I'm not. That

is not what the line of questioning is about.

MR BEAR: It is not clear to me. If you ask somebody --

MR NASH: I think I will finish my cross-examination and then we can make submissions on the point.

MR JUSTICE BURTON: Yes.

MR NASH: Can we look, please, at the tables, Professor Sandercock, and I would like you to take, them, please, from the shell tables rather than your schedules. If we go to core bundle 2, behind tab 18.

A. Core bundle 2, tab 18. Okay, just a minute. Sorry, tab 18, did you say?

Q. Tab 18?

A. Under tab 18 I have the second interim analysis, I thought you wanted me to look at the shell tables.

Q. I am going to take you within there to page 2770, I think, first of all?

A. 2770, yes.

Q. And this is, I think, your table 2B, your disability rating table?

A. DRS.

Q. DRS, yes. Is that the table which you call 2B exhibited to your statement, yes?

A. That is correct. The numbers from the DRS and Hireos were extracted, I hope, without typographical errors into table 2B.

Q. And Hireos is at 2768, if you go back two pages, bottom of the page?
A. Yes, okay.
Q. Now, in relation to both of these tables, Hireos, there is a note that there are 11 missing values for this variable, and then at 2770 it is noted that there are 31 missing values for this variable. Now, isn't that a matter which would have caused you concern about the quality of this data?
A. Well, if the missingness was uneven across the treatment groups, yes. If not, no.
Q. Are you able to detect from these tables whether the missingness is evenly distributed or not?
A. We were assured by Tony Brady that it wasn't.
Q. When was that assurance given?
A. Well, during the call, because he was in the teleconference. I mean -- okay, sorry, yes. Sorry, I should correct my statement. To my recollection, Tony Brady said the missingness was not unevenly distributed between the treatment groups. As with any other form of error, provided it is not unevenly distributed, it doesn't introduce bias, some degree of missing data doesn't matter. And with the advice of the statistician, Professor Stephen Senn, we accepted that this analysis had some missing data, but was nonetheless

informative.

Q. Now, you suggest in your annexure, I think, that the Hireos result in particular is statistically significant. Do you mean by that that if this result was reproduced in a large population it would be statistically significant, or do you suggest it is statistically significant even though it is from a very limited population?

A. I have to bow to -- because the statistical tests, as you can see, are very complicated, and -- can I go back a stage. There are two questions in judging the reliability of the Hireos analyses, my Lord. One of these is, as I was asked earlier, on the assumption was the severity of the head injuries, the traumatic brain injuries approximately similar across the different treatment groups, and you may recall that I said that if you have a proper method of randomisation in general that will assure an even distribution of severity between the different treatment groups.

However, when the number of subjects in the trial is small, some degree of an imbalance may occur, and our discussions focused on a statistical analysis called adjustment by baseline severity, because Tony Brady pointed out that there were slight imbalances in the degree of severity and therefore our assessment of the

statistical significance of the Hireos result had to be done in two different ways, one with and one without an adjustment for the very slight degrees of imbalance in baseline severity.

If under those circumstances you get about the same result with and without adjustment that does suggest that this result is important, and my understanding of the statistical analysis, or the statistical interpretation that Professor Stephen Senn made of these data was that that was indeed statistically significant in its own right, and if confirmed in a larger trial would suggest this treatment was not only statistically significantly hazardous but clinically significantly hazardous; that means it would pose a threat to public health.

In these circumstances we have to separate statistical significance -- which, as you say, in small circumstances may not be a perfect indicator of the effects of treatment. But to the best of our abilities, and after due consideration of the complexities of the statistics, the view taken by our statistical expert, Professor Stephen Senn was that these data were not likely to have arisen by the play of chance.

Q. Can we go on to your table 2C, 2771?

A. I do apologise to the court for the typographical errors

in the initial submission.

MR JUSTICE BURTON: We are looking at --

A. Yes, I know, but the transposition into table C.

MR JUSTICE BURTON: Yes, 277 ...?

MR NASH: 2771.

A. Yes, I have that in front of me.

Q. "... or cause mortality as to day 15", and indeed four missing values for this variable; is that not a matter that would cause concern?

A. No.

Q. These are four deaths, Professor, so it looks as if four deaths have gone missing from the database. Why is that not a matter of concern?

A. No, it is not four deaths are missing, it is whether the patient is dead or alive is unknown, would be my interpretation of this particular point, which I would submit is a different matter. Their status at day 15 is as yet unknown. That is not bad for a trial that is going at this pace.

Q. You make a relationship between this table and table 5, and I think for this purpose we do actually need to see your commentary annexed to your witness statement?

A. So table 2C from my commentary?

Q. Table 2C, yes. I am referring -- incidentally, you will notice, I think, another typographical error in your

table, even the revised version, Professor?

A. I do apologise for that.

Q. Not at all, but I will point it out to you. Status at day 15, under the heading "drugs", the middle table, 21 and 78 together make 99, not 95?

A. I do apologise for that. Yes, that is correct. There is one remaining typographical error.

Q. Not a key point, Professor.

If we go to the note --

A. Well, if you are dead, I suppose it is.

Q. Yes. Note:

"The numbers of deaths is smaller than the number of deaths in table 5, serious adverse events, since the latter includes deaths which might have occurred at any time after randomisation."

And then you say you sought to compare like with like, "hence this table was the more important".

It follows from that that in your view death is to be regarded as a serious adverse event; is that right?

A. I think that is incontestable. Death is an adverse event.

Q. A serious adverse event within the definition of the trial protocol?

A. Well, death is death. I mean, in analysing the effects of a treatment death is pretty important, whether it is

categorised as a serious adverse event or not. I mean, the complexities around serious adverse events that are linked to deaths is a matter for pharmacovigilance, because somebody can have several adverse events and die or somebody can just die.

So for simplicity counting the number of deaths, whether or not they were counted as serious adverse events, is the simplest and clearest way to assess what the treatment is -- one aspect of the treatment's effects.

Q. The point I am driving at, Professor, and I think you agree with it, is for the purposes of this trial death is to be regarded as a serious adverse event, within the meaning of that term in the protocol?

A. You mean there is some degree of double-counting between the analysis of serious adverse events and the effect on death?

Q. No, I mean simply that death for these purposes must be death other than normal death in the course of TBI?

A. Can you repeat the question?

MR JUSTICE BURTON: Are you dealing what I thought we had put to bed, namely that you can have a patient who dies, who thereby suffers more than one serious adverse event. You are not revisiting that?

MR NASH: I am not revisiting that, my Lord, I understand

that entirely.

I am simply seeking to establish with Professor Sandercock that for the purposes of this protocol for death to count as a serious adverse event it must be the outcome of an untoward medical event?

A. No, this is death from all causes, whether or not -- this is death from any cause --

Q. I am sorry --

A. It is as clear as it gets.

MR JUSTICE BURTON: If, for example, the person is taking part in the trial and walks out of the door and something drops on him in the hospital and he dies, that would count, would it?

A. That would indeed. And that is what called part of an intention to treat analysis, which is what this was. It is part of the -- in any clinical trial, once a patient is in the trial they are irrevocably in it, unless they withdraw their consent to continue to participate. On the assumption that all of these patients had not withdrawn their consent to participate in the trial, if it so happens that somebody dies from some cause quite unrelated --

MR JUSTICE BURTON: Car accident on the way to the hospital.

A. Car accident, that would still have to be counted, because that is the nature of an intention to treat

analysis. We can go into why you do intention to treat analysis.

MR JUSTICE BURTON: I hope we don't have to.

A. I would prefer not to, but let's say the constraint that is placed on this analysis is death from any cause, because the protocol said this would be an intention to treat analysis, has to be counted in this analysis whether or not it was related to study treatment or traumatic brain injury, and there are very good scientific reasons for doing that.

MR JUSTICE BURTON: And you knew that.

A. We knew that, indeed, and the tables are labelled "Intention to treat analysis".

MR NASH: Can we go, please, to the adverse trends table, which is at 2761.

MR JUSTICE BURTON: Where are they labelled "Intention to treat"? I can see they are labelled "Deaths from all causes".

A. It says table 7, page 3765.

MR JUSTICE BURTON: Thank you.

A. "Outcome measurements for efficacy by intention to treat", and you will see there are some subsequent tables which are labelled "per protocol", which were of no interest to us.

MR JUSTICE BURTON: Yes, thank you.

MR NASH: Now, you have made the point back at 2761 -- now we are on the equivalent of your table 2A, patients with at least one serious adverse event. You have made the point already that there is a --

A. Sorry, which part of the table?

Q. Top of the page, "Patients with at least one serious adverse event"?

A. Sorry, we are talking about table 2A, not page 2771.

MR JUSTICE BURTON: 2761.

MR NASH: I am so sorry --

MR JUSTICE BURTON: No, you did say 2761.

A. Sorry, which?

MR NASH: Top of the page, I think.

A. Okay, patients with at least one serious adverse event, yes.

Q. You have made the point already, that between the placebo group where you have an incidence of 10.26 per cent death, and all groups, all treatment groups --

A. Patients --

Q. I am sorry?

A. At least one serious adverse event.

Q. Exactly, and all dose combined 33.66 per cent that that is a very stark difference to your eyes; is that right?

A. Correct.

Q. This extreme evidence of a potential harmful effect is unusual in a drug which has been tested safe in pre-clinical, is it not?
A. No.
Q. Is it not improbable that across the treatment population as a whole this level of difference will be reproduced?
A. Well, the prior knowledge we have in the limited number of patients in which this class of drug had been used, and I point out that the data and safety monitoring committee had asked Professor Roberts to prepare a systematic review of all previous trials of this agent had suggested there might be a small reduction in the risk of death. That was the only evidence available to us on really major outcomes in patients with brain injury treated with this drug.

So indeed given the knowledge that the severity of the strokes -- of the head injuries was, as far as we could understand, more or less similar across the four treatment groups, it was highly implausible that this result was due to the play of chance, some baseline imbalance, and the most likely explanation, although I accept not the only one, the most likely, was that it was an effect of treatment, the drug.
Q. Your understanding of this table, Professor, is that it

represents patients who are suffering SAEs which are not TBI related, is that correct?

A. I don't think it really matters whether they are considered to be related to the TBI or not, to be frank. These are adverse events, these are bad things that are serious.

Q. But the protocol requires that an SAE should be an untoward occurrence of the requisite severity, doesn't it?

A. Yes.

Q. So where you have a table which lists patients with at least one serious adverse event within this trial, that means patients who are suffering SAEs other than those which would arise as a result of TBI. You follow that, don't you?

A. I follow the logic, but in looking at these events what we have is -- these are the events that were reported. Now, we cannot comment on the process of how these diagnoses were arrived at, as to whether that process of deciding whether this could be attributed to the brain injury or not. We have no means of checking that. We look at the data that is put in front of us. So we, as data and safety monitoring committee, cannot assure ourselves that the attribution of, was this related to the head injury or not, was correct.

What we have to do is to look at the data that are presented to us.

As I have said already, the adverse event data were not the sole criteria for us reaching our decision, it was just part of what led us to reach our decision, so --

Q. When you are looking at this table, Professor, you know that there is an ongoing cleaning process in relation to the data, don't you?

A. Yes, and we also know that the number of serious adverse events might change quite radically. But it seemed very unlikely that the distribution -- so that the total number might change, I completely accept that. The attribution of cause might change, I accept that. But it seems most unlikely that the distribution between the groups would alter as a result of the cleaning process.

Q. We now know, for example, that there are five patients in the group included in this table, whose SAEs were not serious, so they would drop out of the class all together, they only had one SAE?

A. How are those distributed between the treatment groups?

Q. I can't tell you that, Professor, I am just telling you that fact, and suggesting to you that if they were redistributed that would have an immediate effect on the figures, obviously?

MR JUSTICE BURTON: When you say "we now know", Mr~Nash, where do we get it from? I have seen it in your schedule? Where do we go for that?

A. If I make a quick calculation, if we were to subtract those five from the treatment group, shall we perhaps do that, it would still mean that there was a substantial, I can't calculate the statistical significance -- even if we made the extreme assumption that they were all in the Anatibant treatment group you would still end up concluding there were more SAEs --

Q. But those, sort of, changes to the data as you go through the cleaning process has the potential for altering the figures in the table --

A. All the more reason for getting through the cleaning process as quickly as possible once recruitment had been suspended, and that didn't happen.

Q. You talk in your statement, Professor, of small errors, small variabilities, not making any difference to the overall statistical analysis, but it is obvious, isn't it, that that is a question of degree?

A. Yes.

Q. You have a small population, then comparatively small numerical errors may nonetheless skew the result?

A. Are you suggesting that the data monitoring committee were not aware of that possibility?

Q. I am suggesting that until you know with more precision how much cleaning has been gone through you are not in a position to make a proper safety judgment in relation to the data. So you have made the safety first decision?

A. Yes, I couldn't agree with you more, so what the data monitoring committee have to do is decide on the basis of the data in front of them, and then request that the data be cleaned as quickly as possible, and that didn't happen, because there was interference with the process of collecting the data.

Q. You made the safety first decision, Professor --

A. And that wasn't contested.

Q. It is not criticised?

A. What was contested, what was obstructed was the collection of the safety data in these patients who had given their consent to take part in a research study, and I regard that as completely unethical. For legal reasons and for commercial reasons, a group of altruistic people, 220 people, who have put their lives at risk to try and answer a medically important question and Xytis, for financial reasons which are made quite clear in their dispositions, have decided to delay the collection of important safety data on these patients, put me in an invidious position, my Lord, and I have to

protest, I really do. I mean, I'm a doctor, I look after patients who are sick, where we are trying to find effective treatments for them, and I really find this very distressing that at the time when we had major concerns about these volunteers who had agreed to join the study for no financial gain should have their altruistic gesture negated by a base financial manoeuvre to try to increase the profits of Xytis, I really found that most objectionable. I am sorry, I shouldn't have said that, I'm terribly sorry. I really care about patients, I really care about clinical trials and good science, and I just feel that this is not appropriate.

Can I have a glass of water, please, I just need to collect myself.

I have worked in clinical trials for 25 years and I have never seen anything like this behaviour before, I have always striven to collect data, to provide reliable answers to important medical questions and I have never seen anything like this before. I find it deeply distressing.

Q. Professor, I have no further questions.

MR JUSTICE BURTON: In that context it causes me to ask whether the position at lunchtime is irrevocably altered or whether we have simply taken in Professor Sandercock because we had to do so.

MR NASH: I am not sure of the very latest on that, my Lord, but --

MR JUSTICE BURTON: No doubt what he said will have been take account of.

A. Thank you, my Lord. I'm sorry for the outburst.

MR JUSTICE BURTON: No, it was valuable that you said it.

MR BEAR: Could I indicate -- we are not going to do it now, but on Monday morning I intend to make a further application for security for costs.

MR JUSTICE BURTON: Two things arise.

The first is your schedule, Mr Nash. I mean, you didn't ask about med -- what is it called -- let me just find it. MedDRA.

MR NASH: MedDRA.

MR JUSTICE BURTON: MedDRA coding which, as I say, is new to me, I don't know whether I should, but at any rate, at least in my present judgment, and I haven't even heard Mr~Bear~--

A. May I comment, my Lord?

MR JUSTICE BURTON: Yes, of course, do in a moment. B(a), B(f), B(g) and B(h) Seem to me to fall outside what I have any understanding of in relation to this litigation.

MR NASH: I'm sorry, could you run through those again?

MR JUSTICE BURTON: B(a), B(f), B(g) and B(h). There may be

others.

MR BEAR: Your Lordship has a different document from mine, I'm afraid, I don't have a B(f).

MR JUSTICE BURTON: B(a):

"Validated duplicate or incompletely reviewed entries."

B(f):

"Inadequate tracking of queries."

B(g):

"Failure to effect a second data entry."

B(h):

"Failure to fully implement MedDRA coding."

MR BEAR: I do have the same document, with some additions, I think these are, in fact, 2(b), then 2(f) and 2(g).

MR JUSTICE BURTON: So be it. At least those seem to be wholly new, certainly to me, but there may be more.

I do urge a full appreciation of the need to particularise what the case is. If the case is: failure to reconcile -- which is how it started -- the SAE forms and the CRF forms, then the answers that have been given to you, at any rate so far, have not been very helpful.

That case at least I understand, but if there is anything else, it really does need to be formulated.

MR NASH: I understand.

MR JUSTICE BURTON: I am concerned about the suggestion that

there is a second supplementary report which has not been served yet, it has not come before me in the sense that I am not prejudice because my document does not refer to it, but Mr Bear apparently does. There has to be some organisation here. Not criticising at all.

You wanted to say something about MedDRA or indeed otherwise?

A. Yes, I mean MedDRA is a form of coding that occurs later in the process of looking at events. If somebody is dead, they are dead, and that is why death from all causes is a simple and robust measure of effect.

Thank you for your patience.

MR JUSTICE BURTON: Can I understand, did you -- if it is the case that they didn't fully implement MedDRA coding by the time it got to you on 1st November, is that something you knew, and would that have made any difference?

A. We were not aware of the MedDRA coding status, but it would have made no difference to our interpretation of the results, or our decision making. It was not material.

MR JUSTICE BURTON: Yes, thank you.

Do you have any re-examination?

MR BEAR: No, my Lord.

MR JUSTICE BURTON: Thank you very much indeed.

Discussion re housekeeping

The other question, of course, is timing. We are going to have to think about whether we are going to finish next week.

MR BEAR: If every point is still pursued, we won't finish next week.

MR JUSTICE BURTON: And Mrs Shakur, of course, is going to take some time, you have told me that. But we have fallen behind, because of this morning, I am not critical of that in the slightest, but the fact is that has happened. So we are going to have to think about -- I think I can probably be permitted to go into the following week, because it was probably going to be allocated to me for judgment writing, but whether you two are available, or your witnesses -- at any rate for Monday morning there will need to be a reconsidered timescale.

MR BEAR: My Lord, I think we are still waiting, I~will be corrected if I am wrong and apologies if I am, for a document indicating on the database development of Ms Wells and Mr Montgomery issues. Your Lordship asked for that on Day 1 and we haven't had it, and it does make the conduct --

MR JUSTICE BURTON: It looks as if this document was a conglomerate, because if there is a reference to

Mrs Wells' supplementary in relation to (h), then it looks as though -- this may or may not be the final version. But at any rate whether there has to be a second document or not is a matter for to you think about.

MR BEAR: I reserve my position obviously on whether this is appropriate --

MR JUSTICE BURTON: If there are things that are outside the pleading, even at this late stage, then that is a matter of concern.

MR BEAR: Yes, my Lord.

MR JUSTICE BURTON: 10.30 Monday.

(5.05 pm)

(The court adjourned until 10.30 am on Monday, 3rd March 2008)

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