Wednesday, 27th February 2008

(10.30 am)

MR NASH: My Lord, just one matter of housekeeping before we get to evidence.

Discussion re confidentiality

You will recall there's outstanding the question of the confidentiality order.

MR JUSTICE BURTON: Yes.

MR NASH: I'm afraid there is a disagreement in relation to that, and it's this: although in principle there's no difficulty with confidentiality as against the world, you will recall that under the terms of the CTSA the information which was produced from this trial belongs to Xytis, and indeed one of the reliefs we are seeking in this proceeding is to get the information delivered.

So the order should reflect the fact that once Xytis has the information, Xytis is entitled to use that information for its own purposes as it sees fit, and, therefore, there shouldn't be any restriction in the order as against Xytis.

MR JUSTICE BURTON: Does this depend upon whether the agreement is terminated?

MR NASH: Well, the delivery-up obligation depends on that.

MR JUSTICE BURTON: Surely, yes.

MR NASH: But the principle that the information produced

from this trial belongs to Xytis doesn't depend on termination of the agreement. That's encapsulated in the agreement.

MR JUSTICE BURTON: Yes. What's the form of order that you want?

MR NASH: Perhaps we can pass up a draft?

MR JUSTICE BURTON: Can I see what the disagreement is about?

MR BEAR: Would it help to see ours as well?

MR JUSTICE BURTON: Yes.

MR NASH: I think it's all in one document. What we've done is used your --

MR JUSTICE BURTON: The rival versions are in one document?

MR NASH: The rival versions, yes.

MR JUSTICE BURTON: Thank you so much.

MR NASH: It's really the first paragraph that is the particularly contentious paragraph, and you will be able to see through the deletion that we've put in that what the school want is a general restriction, I think for all time --

MR JUSTICE BURTON: Hold on, where -- it's supposed to start --

MR NASH: On page 1.

MR JUSTICE BURTON: Page 1, and the whole of that is deleted?

MR NASH: Yes, and that's a deletion by us.

MR JUSTICE BURTON: So let me read -- this is the version by Mr Bear:

"Notwithstanding ... it is ordered that the evidence ... may not be used other than for the purpose of these proceedings."

The shell tables, the witness statement and the transcript and the copies.

You say:

"The claimant's solicitors shall be permitted to provide Dr Vincent Simmon of the claimant with any document falling within the following categories ..."

You don't like the defendant's objections being noted. And then you set it out.

MR NASH: I think the objection point we don't feel particularly strongly about, so I don't think we'll fall out over that.

MR JUSTICE BURTON: No, and then paragraph 2.7:

"... shall be varied to permit access by the claimant to the database copies. No persons shall print or publish the unblinded trial data or any witness statement or transcript."

You've taken out the whole of 1 because it might affect you, but you've put it back in again -- well, you help me. What is the difference between the two of you

as reflected in this document?

MR NASH: The difference is that paragraph 1 as it stands is a general prohibition on use of the material which is disclosed during the course of this trial.

MR JUSTICE BURTON: Other than for the purpose of these proceedings?

MR NASH: Other than for the purpose of these proceedings.

MR JUSTICE BURTON: Right.

MR NASH: That includes both the shell tables particularly and you'll see at (d) also the copy of the clinical trial database and the hard copy output of that database.

MR JUSTICE BURTON: Right.

MR NASH: We say that that material ultimately belongs to Xytis under the terms of the trial agreement and there should be no restriction on Xytis's use of that.

MR JUSTICE BURTON: But the objection we're dealing with at the moment is that it's unblinded, and you shouldn't see until the termination of the trial -- whether you own it or not -- you shouldn't see it in unblinded form, except that you're being allowed to for the purpose of this litigation?

MR NASH: Yes, but the point --

MR JUSTICE BURTON: So once the litigation is over, you can't see it unblinded until the end of the trial.

After the end of the trial, of course you could see it unblinded, because it's yours.

So we are only surely dealing with the period of the trial, aren't we?

MR NASH: Well, the unblinding point, my Lord, I think goes back in part to what we were discussing yesterday, that ultimately if the unblinding is compromised then that's a difficulty for us rather than for the school, but in any event what is happening at the moment is, as we understand it, data is being processed and so forth, that would produce a body of information relating to the trial population as it presently stands.

MR JUSTICE BURTON: Your paragraph 2 is limited to Dr Simmon and that's all you want for the purpose of the litigation?

MR NASH: Oh yes.

MR JUSTICE BURTON: That's fine, and that protects everybody because we've got -- insofar as anybody can be protected, there's a special exemption for Dr Simmon and you're going to be able to say to the regulatory authorities: it was only one person and it was under this sanction, et cetera, et cetera.

But all I'm really saying is: for me to make an order exempting you in relation to unblinded material generally wouldn't help you at all, it's not what you

are wanting.

All you need is the protection for the fact that once the trial is finished, then the material can be unblinded and of course you can have it, because it's yours. We just want to have some protection there.

MR NASH: There are two different points, my Lord.

The second paragraph -- which is now the first paragraph -- is the unblinded point, and there's no difficulty about that. The first paragraph is:

"A general restriction for all time ..."

-- you'll see in the first paragraph:

"... may not be used or further disclosed for any purpose [that material]."

If that stays in place, that means that Xytis will not be entitled, ever, to use or to have access to not simply witness evidence, transcripts of oral evidence, but also shell tables and clinical trial databases.

MR JUSTICE BURTON: I see that, but you don't want that until the end of the trial anyway.

MR NASH: Xytis shouldn't be under -- we, Xytis, are not going to call for unblinded material save to the extent specified in the second paragraph.

MR JUSTICE BURTON: Yes, but it is unblinded. I mean, that's the problem. If we're talking about (a) in particular, it is unblinded. (d) may fall into

a different category, because the database copies are blinded, aren't they?

MR NASH: The database copy is blinded, my Lord, yes, I think I'm not making the distinction sufficiently clear.

Paragraph 1 is the general restriction on the use of material.

MR JUSTICE BURTON: I'm seeing that, but you should be prevented from -- and you want to be prevented from making any use or seeing it or any of that kind, (a), in case it could be suggested that there's some risk to the blinded material, but only of course until the end of the trial when of course you're entitled to it, because it's yours.

Any protection there needs to be in would simply be the fact that once the trial is over of course you, unlike anyone else, can have access to unblinded material.

I'm finding it difficult to understand your problem. You want to ensure that once you're entitled to see this material in unblinded form, which is at the end of the trial, you should not in any way be hampered by -- or in breach of this order. That's understood and some kind of wording which makes that clear can be incorporated. But I can't see any other problem.

MR NASH: Well, I think that provided it's clear that we're entitled under our contractual rights to have the material and to use it as we see fit at the appropriate time, I don't think there's a difficulty. I'm going to take an instruction, because I can see my solicitor is anxious about this.

MR JUSTICE BURTON: Yes. This will be a saving by reference to the clause of the agreement. (Pause).

What's the clause of the agreement which makes it clear that you are entitled to these materials and that you're entitled to it unblinded once the trial is at an end?

MR NASH: There's -- well, there's the provision entitling to us call for the information at the end of the agreement, which is at the bottom of page 12, clause 9.4 --

MR JUSTICE BURTON: Yes. What about the unblinding position?

MR NASH: -- and there is also the general provision -- there's a confidentiality obligation in our favour at article 4:

"In view of the proprietary rights and interests of Xytis ..."

If you will bear with me, my Lord, I believe also there's a general provision that we are the owners of

the information.

MR JUSTICE BURTON: What I was thinking was that, if one could insert into their paragraph 1 "subject to the claimant's rights under clauses X, Y and Z", then that would protect you.

MR NASH: Yes, I think that formula would suffice in fact, yes.

MR JUSTICE BURTON: Mr Bear?

MR BEAR: And probably lead to endless argument. That's the difficulty.

MR JUSTICE BURTON: Why?

MR BEAR: Well, unless we're completely sure between us about what those clauses mean. If we are, then we might as well say so in the order.

MR JUSTICE BURTON: Why don't we, instead of wasting time now, see if you can reach some formula? I am quite clear, unless there's any matter of principle that you are putting forward, that Xytis are entitled to -- certainly on termination of the agreement -- to all these documents, if the agreement is ever terminated, and certainly to the unblinded material once the trial is over, and I don't wanted to find that any order I make in paragraph 1 which is intended to protect both of you against the world and both of you to an extent, although primarily him, against the regulator, so far as

the period when everybody wants this information to remain blinded, should by a side wind, interfere with their rights to see the unblinded material at the end of the trial.

MR BEAR: At the end of the trial is the key point, because of course just to correct what my learned friend has said, that this consistent position that it's entirely a matter for Xytis, that isn't really accurate. What happens is that people -- individual subjects around the world -- are asked to take part in a potentially risky drug trial, and they are asked to do that, and this isn't just some empty piety for the good of mankind generally, and that's what the documents make quite clear.

The covenant, if you like, between the trial subject and those who run the trial, is that the matter will be dealt with properly and eventually there will be a published report which can be looked at by doctors around the world.

So simply to say "we want to take the risk that none of this is going to be of any use" is a breach of faith to the trial patients, and that affects my clients -- as well as them having a legitimate concern about that in itself -- because they have recruited all these hospitals around the world, it's their network bar one

or two, which is actually running a trial on the ground.

MR JUSTICE BURTON: It may be if you can't reach agreement on some wording we will have to have a general provision which might still lead to further argument, but what I don't want to do -- because I don't want to take time on this -- is by virtue of doing two things which we all agreed was our aim, which was protecting everybody against the world and protecting the blinded material for the duration of the trial, that we then have arguments about matters which are not at the moment in issue.

MR BEAR: At the end of the trial, obviously everything becomes unblinded. There's only one exception to that which is not of interest, Xytis say, which is Mr Brady's or Sealed Envelope's proprietary software, which is within a different category although it's within the order.

MR JUSTICE BURTON: Yes.

MR BEAR: Apart from that obviously at the end of the trial it's all opened up.

MR JUSTICE BURTON: Good, I'm sure some wording can be agreed.

MR BEAR: Yes, my Lord.

MR NASH: Just to complete the point, article 5 of the agreement is the article I was looking for, and it's the

one that says in terms, and plain terms, the material belongs to us. That is what we are seeking.

MR JUSTICE BURTON: Yes. Well, either if you're both confident that there are no outstanding disagreements between you we can simply cross-refer to the relevant articles and say that it's not intended to -- either subject to those clauses or it's not intended to interfere with your rights under those clauses or something of that kind, or if there's any disagreement, then just spelling out the principles that we've been enunciating in the last ten minutes, namely that this is not intended to interfere with your rights, and it's not intended to interfere with your rights to see the blinded material once the trial is completed.

MR BEAR: Can I just mention one point so that we don't get taken by surprise during the evidence?

I am going to be asking Dr Goedkoop, if I'm pronouncing his name correctly -- apologies if I'm not -- about some of the unblinded tables.

MR JUSTICE BURTON: Yes.

MR BEAR: I'm going to assume that when I do that, everyone apart from Mr Simmon on the claimant's side --

MR JUSTICE BURTON: Is out of court?

MR BEAR: -- and everyone who's not on the TSC on our side is out of the room.

MR JUSTICE BURTON: That's very sensible. Is that all right?

MR NASH: I'm sure that's fine.

MR BEAR: Legal advisers obviously are in a different position.

MR JUSTICE BURTON: Yes. Thank you very much.

MR NASH: My Lord, we call Dr Goedkoop.

DR RENE~GOEDKOOP (affirmed)

Examination-in-chief by MR NASH

MR JUSTICE BURTON: You can either stand up or sit down, whichever you prefer, or you can start doing one and change to the other, whichever you like.

A. It depends on the length of yes, sir.

MR JUSTICE BURTON: If you can speak up very clearly so everybody in the back of the court can hear what you say.

A. Yes.

MR NASH: Would you give the court your full name, please, Dr Goedkoop?

A. My name is Rene Goedkoop. It's a Dutch name, so the pronunciation is difficult, I understand.

Q. Your address, please?

A. It's 14 Chemin des Buissons, Rond in Bogis Bossey, which is in Switzerland close to Geneva.

Q. Dr Goedkoop, there are a lot of files around you, and

I'd like you to try to find witness statement file 1. It may be that you need some help with these files.

MR JUSTICE BURTON: Yes, is it possible to have someone from each side's solicitors sitting down there or sitting next to the witness who can help them clear away the files as they finish and help them find the file. Thank you very much indeed.

If you can keep a good look up the top from down where you are, and help the witness find the bundles. With luck, we're going to be able to stick to the ones up there, but not necessarily, because not all the important documents have been transferred to the core.

MR NASH: In that bundle behind tab 2, please, Dr Goedkoop, there is a copy witness statement. I'd like you just to look at that quickly and confirm that it's your evidence for the purpose of these proceedings.

A. Correct, and I signed it as such.

Q. And so far as you are aware, is everything that you say in that statement correct?

A. Correct.

Q. Would you also take up witness statement bundle number 2 and look behind tab 17 within that bundle, and again would you confirm, please, that that was a statement which you made previously on 13th September of last year for these proceedings?

A. That's correct.
Q. And again, so far as you are aware, is everything in that statement correct?
A. Correct.
MR JUSTICE BURTON: Now, my problem, Mr Nash, is that I've only read the second witness statement, because that's all I was asked to read. I don't know if there's anything substantial in the first witness statement, whether perhaps you should draw my attention to it.
MR NASH: I don't think there is, my Lord. I think, particularly with this witness, he largely repeats what he has already said. Formally I wanted that in the evidence.
MR JUSTICE BURTON: Yes, thank you very much.
MR NASH: Can you return, please -- you can put away, I think file number 2, Dr Goedkoop, and I'd like to ask you one or two additional questions.
Could you go, please, to paragraph 10 of your statement? You say there that from various discussions, in the middle part of this paragraph, you were aware of:
"... concerns regarding inconsistent interpretation regarding data fields (in particular SAEs and AEs, related to the underlying traumatic brain injury ... and timing thereof ..."
A little further:

"... concerns over query resolution process, that is the process by which the information from the CRFs would be cleaned)."

Could you explain, please, what your understanding of those concerns were?

A. Well, I think it refers to the notion that I felt there was a disconnect, a discrepancy between the pharmacovigilance database and the database as presented to the DSMB, leaving in the middle which one was right or wrong, and we're not talking about a small discrepancy, but really a large discrepancy that I would think could not be simply explained by a lack of synchronicity of collecting all the data that you get on an ongoing basis in such a trial.

MR JUSTICE BURTON: What do you mean by this? Do you mean that you personally sat down and looked at the two databases and noticed that there were discrepancies, or are you simply saying that you feared that because the two appeared to be kept separate, there might be some discrepancy?

A. No, I've seen the one that was presented to the TSC, so those tables, and I was aware -- because I'm regularly reported on that -- how many serious adverse events are seen by the pharmacovigilance group and reported to the authorities.

MR JUSTICE BURTON: So during the relevant period, you personally were looking at both databases?

A. No, I was only seeing the database during the DSMB -- during the TSC meetings, so the trial steering committee meeting, at November 1, and the HPM that is kind of ongoing monitoring of the activities of the pharmacovigilance --

MR JUSTICE BURTON: Stopping you just for a moment. In paragraph 10 of your statement, you're talking about a period -- you're not talking about a period prior to 1st November?

A. Correct.

MR JUSTICE BURTON: You're saying that in the meeting of the TSC -- I thought that was by telephone?

A. That was a telephone conference, correct.

MR JUSTICE BURTON: So in that meeting, you noticed or were looking at something. What is it you were doing?

A. Okay, I received by email a document containing the tables 5 and 7, and I had some time before the actual start of the telephone conference to briefly walk through the figures, being astounded that it was just bluntly unblinded data without any discussion about this. But what I think is more important, that I did see figures that didn't make sense, so --

MR JUSTICE BURTON: So we are talking about -- I hadn't

realised this -- the difference between 5 and 7, that is the unblinded information, which I personally haven't taken on board yet.

A. Yes.

MR JUSTICE BURTON: Which is that which is annexed to one of the other witness statements?

MR NASH: Well, Dr Goedkoop's particular version of it is in the chronological bundle. I'll come to that if I may in a moment.

MR JUSTICE BURTON: Yes, of course, I just didn't understand -- I do understand -- that what the witness is referring to, as I understand it, is concern about discrepancies, not antedating 1st November, and limited to those which appeared from his comparison of what he was supplied immediately prior to the 1st November meeting. Have I got that right?

MR NASH: I don't think it's quite right, my Lord, I think there are actually two points here, and I'm going to ask Dr Goedkoop, please, just to remind himself of the terms of paragraph 9 and the first part of paragraph 10 of his statement. You talk there about becoming aware of concerns. What period are we talking about there?

A. Here you are referring to drafting a letter, I think, by the end of August, where we had internal discussions at Xytis, where we had a concern about a potential

discrepancy between the number of AEs/SAEs as seen by the London school versus that of the HPM database. That's what you are referring to.

Q. How did you become aware of the potential for discrepancy between the two, in this period, prior to 1st November?

A. It's because Vince Simmon described it to me, that there were numeric differences, not large, but I think there was that risk of discrepancy. This is from a pure reporting point of view, that's a concern, in terms of the regulators, but it's also an issue in terms of collecting the data and creating a backlog, and the larger the discrepancy becomes the less trustworthy either one could become.

MR JUSTICE BURTON: This was just around the time of the 30th August when you knew that --

A. Correct.

MR JUSTICE BURTON: -- Dr Simmon was corresponding about it and he discussed it with you, but you didn't have any personal knowledge at that stage?

A. No, because I'm not interfering with database issues, correct.

MR JUSTICE BURTON: You understood what Dr Simmon said?

A. Correct. It's a --

MR JUSTICE BURTON: That's stage 1, when you were concerned,

is that right?
A. Yes, correct.
MR JUSTICE BURTON: Sorry, you were going to say something, I didn't want to interrupt.
A. Yes, I think it's a well-known phenomenon that there will always be some discrepancy because of the timing and the collection of data, but it doesn't mean that there should be -- this should become uncontrollable, since we have this reporting duty to the authorities in relation to the safety of whatever drug is under investigation.
MR JUSTICE BURTON: So that's the stage 1?
MR NASH: Yes, and in the stage 1 period your knowledge, your direct knowledge, related to the HPM database, is that correct?
A. HPM database and the observations as discussed by Rowland Furcha and by Vince Simmon.
Q. Then phase 2, if we are calling it that, is the meeting of 1st December when you received the unblinded information. At that stage you have knowledge from the HPM database in your head, as it were, as well.
Can we then go to that, please?
A. Yes.
Q. The document -- this is where we're going to start looking at unblinded information, so perhaps those who

can't see it can leave. The document is in the chronological bundle number 8 at page 2243?

MR JUSTICE BURTON: It's not in the core bundle, not yet.

MR NASH: I don't think it is, not yet.

MR JUSTICE BURTON: Right, well, let's transfer it. 2243?

MR NASH: 2243.

MR JUSTICE BURTON: How many pages is it?

MR NASH: It runs through to 2248.

MR JUSTICE BURTON: I at any rate am going to take this out and put it in the core bundle.

MR BEAR: Would it make sense to put it with tab 18, which is the full copy of this material?

MR JUSTICE BURTON: Tab 18 is the?

MR BEAR: It's the DSMB's own print-out that was supplied. It's the same.

MR JUSTICE BURTON: Thank you.

MR NASH: It's the same document without the annotations.

MR BEAR: It should be the same.

MR JUSTICE BURTON: Yes.

MR NASH: No you, Dr Goedkoop, with that document in front of you, can you please explain first of all what we see in this document?

A. You're seeing the tables 5 and 7 as presented to the DSMB.

MR JUSTICE BURTON: Can you speak up a bit?
A. Yes, sure, and so you're seeing the tables as presented to the DSMB and hence to the TSC, tables 5 and 7, and you also see my first knee-jerk reflex annotations after receiving it by email and walking through those figures.

So it's partially intuitive, but I think it's also based on the experience of having seen many databases as being analysed throughout my whole career, in the clinical research set.

MR NASH: We'll return to the first page in a moment, but if we go, please, to 2244, which is the first page with figures on it, the top left-hand side, table 5:

"Adverse events by intention to treat."

A. Correct.
Q. This is really so we understand what we're looking at. The first part of that table, as you read down the left-hand column, gives you the number of adverse events per patient, yes?
A. Correct.
Q. And then there are three figures in a table below that, no adverse events, and that's divided up between the high, medium and low dose groups and placebo, with a total at the end. One or more adverse events, same breakdown, and then a total column.

Then you're given all doses of the drug combined, so

that takes the first three columns of the table above and produces a combined table.

A. Yes, it's called pooled data.

Q. Pooled data.

Then the next line, in the middle of the page:

"Patients with at least one non-serious adverse event but no serious adverse events."

We then have a new set of figures -- so this is a new sub-table as it were -- and again it's worked through in the same way.

Now, looking at your annotations now, please, against the first set of figures you have written "AE/PT" then I think it's a approximation sign, and "N equals 101". Can you explain what that means?

A. Yes, AE per patient, basically it's summarising for myself what this table means, and it basically tells me that independent of the treatment arm the number of AEs are more or less equally distributed. So similar for each dose group, or treatment arm I should say.

Q. Then, into the next table, you have another --

MR JUSTICE BURTON: What does "N equals 101" mean?

A. That's the number of events.

MR JUSTICE BURTON: I see, thank you.

How do you arrive at 101?

A. I have to scratch my mind for that one, just a sec,

please. (Pause).

That's all the patients, so the pooled patients that have received treatment.

MR JUSTICE BURTON: That's the number of patients, yes, I follow.

A. Sorry, the number of adverse events as seen in the treatment arms.

MR JUSTICE BURTON: It's the figure we've got down on the -- under the next column?

A. Correct.

MR JUSTICE BURTON: But it's the number of adverse events per patient in the treated groups?

A. Correct.

MR JUSTICE BURTON: Right.

MR NASH: Then your annotation below that:

"Non-SAE slightly higher ..."

Then a mathematical symbol which I --

A. RX stands for treatment, so the treatment group.

Q. The treatment group?

A. Yes. So that's basically comparing it to placebo.

Q. Right.

A. So small numerical differences, whether that's statistically supported I don't know.

Q. Here we're dealing with non-serious adverse events?

A. Correct.

Q. If we go to the top right-hand corner of the same page, we have a table which records patients with at least one serious adverse event, and against some annotations, perhaps you could explain those.
A. Well, it's for me, in my mind again, to summarise the number of patients that have a -- at least one serious adverse event, and the P stands for placebo and it seems that in the placebo group there are fewer patients with a serious adverse event, at least one serious adverse event, as compared to the active treatment arms.
MR JUSTICE BURTON: So what does P4 mean?
A. Excuse me?
MR JUSTICE BURTON: P4, what does that mean?
A. It's a P with an arrow. So the P stands for placebo and it seems that --
MR JUSTICE BURTON: The placebo is higher?
A. No, well, it's -- to me, there may be a benefit in terms of having less serious adverse events.
MR JUSTICE BURTON: So placebo better off?
A. It seems, yes.
MR NASH: Then again presumably the same annotation at the bottom of the page means the same thing, placebo group is better off as far as non-serious adverse events is concerned?
A. Correct.

Q. We then go over the page within this, 2245, and this is a continuation actually, at the top left-hand corner is a continuation from the previous page, so we're now into a table:

"Patients with at least one serious adverse event which is suspected to be related to the study drug."

A. Yes, and that's really for me a table I had difficulty with, because I've never been involved in considering safety concerns in a study where the adverse event is not attributable or thought to be attributable to study drug.

Q. Can you explain that as a feature of this study?

A. Yes. Normally when one reports serious adverse events or adverse events for that matter, there is always a question of causality: is it study related, is it procedure related, is it treatment related? And this table basically tells us that the serious adverse events, as reported in the previous table, are not related to study drug, and that raises, for me, a red flag.

Q. This table, if we take it from the bottom of 2244, is a table of:

"Patients with at least one serious adverse event which is suspected to be related to study drug."

MR JUSTICE BURTON: Haven't you got it the wrong way round,

Dr Goedkoop, I don't know, is that what you're asking, Mr Nash?

MR NASH: I thought the last comment made by Mr Goedkoop, you had expressed it the wrong way round.

MR JUSTICE BURTON: Yes.

MR NASH: This is a table, it seems, of people who have adverse events which are related or suspected to be related to the study drug, that's right, isn't it?

A. I'm not sure if you --

MR JUSTICE BURTON: The record has you saying this, doctor:

"... this table basically tells us that the serious adverse events reported in the previous table are not related to [the] study drug, and that raises for me a red flag."

In fact that's the wrong way round; they are suspected to be related to the study drug.

A. There's only one serious adverse event that is reported as being related to study drug.

MR JUSTICE BURTON: Yes.

A. So that --

MR JUSTICE BURTON: Why does that raise a red flag?

A. That raises a red flag, because normally one -- the authority, nor we, would judge a compound to be unsafe if there is no relation between the study treatment and the serious adverse event.

MR JUSTICE BURTON: Yes?
A. So if there are serious adverse events, but there is only one thought to be attributed to --
MR JUSTICE BURTON: It says "at least one".
A. At least one.
MR JUSTICE BURTON: Yes?
A. At least one SAE, if I'm correct.
MR JUSTICE BURTON: Yes, I'm not understanding why it raises a red flag, that's all. This is simply recording patients with at least one serious adverse event which the local doctor or investigating officer has concluded on balance is related to the study drug.

Now, I understand why that should raise a red flag with you as a worry about the effect of the drug, but what I don't understand is why it raises a concern for you when you say that you've never been involved in a similar trial before.

Can you explain what you're trying to say to us?
A. Maybe I'm not expressing myself clearly enough. Normally, we look at the causality of the drug and the serious adverse event, or the adverse event.
MR JUSTICE BURTON: Yes.
A. Now, in this case there are serious adverse events, as expected, but only one of those is thought to be attributed -- attributable to study medication.

What that tells me is that the serious adverse events are not related to the study medication.

MR JUSTICE BURTON: The word "at least" is used. They're not isolating one necessarily. It's "at least one".

A. Not the way it's put in the table.

MR JUSTICE BURTON: Well, bottom right-hand corner of page 2244 "patients with at least one" -- I understand what you're saying if you thought it was just one, how on earth could they necessarily reach that conclusion, but it's "at least one".

A. Are we on the same page, or --

MR JUSTICE BURTON: You're not looking at the right place. I saw your finger in the wrong place. Page 2244.

A. Okay.

MR JUSTICE BURTON: Bottom right-hand corner.

A. Yes.

MR JUSTICE BURTON: Now, that is the heading we're looking at, but it happens -- no, your finger is too high. There you are, that's it. That's the heading which happens to go on to the next page.

A. Yes.

MR JUSTICE BURTON: That's what you're being asked about.

MR NASH: The heading in the bottom right, Dr Goedkoop, is the heading to the table we then see over the page.

A. Yes.

Q. And you've told us that there was some feature of the table at the top of 2245 which caused you -- which raised a red flag. I'm just trying to identify what that feature is.
A. So, again, it talks about:
"Patients with at least one serious adverse event which is suspected to be related to study drug."
Q. Yes --
MR JUSTICE BURTON: You're then going to the left-hand side when I think you should stay on the right. Am I right, Mr Nash? Is this running down left hand and right hand?
MR NASH: No, I think --
MR JUSTICE BURTON: Where do we go from the bottom right-hand corner of page 2245 with the heading? Do we then carry on on the next page on the right-hand side or do we carry on on the left-hand side?
MR NASH: I think we carry on on the left-hand side.
MR JUSTICE BURTON: Do we?
A. Left-hand top, and if we look at the row which says "yes", there's only one 1 in that line. So it means there are serious adverse events, but only in one instance it was thought to be attributable to study drug. So, in fact, I don't want to be repetitive, but it's what I intended to say before, and to me that raises a red flag, because I would never take a decision

on serious adverse events that are not thought to be attributable to study drug, except in case of a preponderance of a specific serious adverse event. But that's another story.

MR NASH: So the red flag you're referring to in relation to this table is the fact that there is only one suspected serious adverse event, suspected to relate to the study drug?

A. Correct.

Q. The red flag is: we shouldn't be making decisions as a result of that piece of information?

A. It's one of the red flags in my mind that contributed to my statement.

Q. I understand?

MR JUSTICE BURTON: That's nothing to do with discrepancies, is it?

A. No, because I have --

MR JUSTICE BURTON: I'm not sure whether it's an issue in the trial, then. This is on outcomes. This is the outcomes aspect, Mr Nash, isn't it?

MR NASH: This is the adverse event data.

MR JUSTICE BURTON: But this relates to the second the -- no?

MR NASH: That is the efficacy question, and that is table 7 which --

MR JUSTICE BURTON: This is saying: well, if there's only one patient out of all this number -- out of these 100 patients -- in respect of whom there is -- it is feared that there may be an SAE related to the drug, what are we fussing about? It's not a danger, it's not a risk, why are we stopping the trial? I can understand all that, but it doesn't seem to go to the issue in our trial which relates to discrepancies and incorrect recording of SAEs.

MR NASH: Well, it is associated with that question, my Lord, because -- well, I don't want to start making submissions while the witness is in the box giving evidence. But I'll explain that in a moment.

MR JUSTICE BURTON: Anyway, the witness has said, no, this has nothing to do with the discrepancies, that's right, isn't it?

A. No, that's not what I said.

MR JUSTICE BURTON: Let's just see what you said and then we'll come back to it. Hold on. You answered -- can you read out my question and answer relating to when I thought I had said to the witness -- and I thought he agreed -- that this point he was now making had nothing to do with discrepancies?

MR NASH: You asked:

"That's nothing to do with discrepancies, is it?

"Answer: No, because I have --"

Then the answer was interrupted.

MR JUSTICE BURTON: I cut in too quickly. So you said to me, I thought, that your red flag -- which I perfectly well understand, I think, in the light of what you've just said -- doesn't have anything to do with your concern about discrepancies, and you said, no, it didn't, but if you want to correct that, this is your moment.

A. I think the interpretation I gave on the table is really related to the table. Whether there are underlying discrepancies in the database contributing to the figures in these tables, at that moment that was not my immediate concern.

MR JUSTICE BURTON: There it is, right.

MR NASH: Can we move on, please, from that table, Dr Goedkoop? You then have a number of non-serious adverse events, and you've annotated that with the approximation sign again, I think, is that right?

A. Correct.

Q. What did you mean by that?

A. Well, that it's kind of similar amongst the four treatment arms, and the next line, "what about related", that of course has my curiosity, well, what about relationship to the non-serious adverse events, because

if there is some kind of preponderance there, that could actually add to the conclusion.

Q. The relationship there is between the non-serious adverse events and the drug, is that right?

A. Correct.

Q. Yes.

Then I think we'd better just have the table at the bottom of the left-hand column:

"Number of serious adverse events."

You've annotated SAE, again approximate. Does that signify, similarly, approximately the same within each group?

A. Yes, correct.

Q. Then in the right-hand set of columns:

"Number of serious adverse events by category.

"Note: each patient can have more than one event in each category."

And you have written against that:

"What about causality" and also "Very clear".

Can you explain those annotations?

A. The "What about causality" reflects to the kind of more extensive discussion we just had about the table on the left-hand corner of the same page, 2245.

MR JUSTICE BURTON: Can I interrupt there? Does not causality at any rate on the face of the statistics

speak for itself if all the events are higher in the drug groups rather than in the placebo groups?

A. Not necessarily, I tend to agree with you that this could be the case, but that really depends on how these serious adverse events are distributed and how the number of serious events were accumulated, and the reason I raise that question and the question mark is there is because I knew from the pharmacovigilance database of HPM that there was a distinct number of deaths, and that was definitely in the top of my mind, which is more or less similar to what is presented in this table, but the interesting part of it is that on one of the previous pages it is stated that there are 38 patients with serious adverse events, but to my astonishment -- and this was of course my first knee-jerk reflex -- there were 32 death reported. I know I'm a medical doctor, but we cannot make wonders in this case, you cannot have patients die over and over again, because here are more death reported than number of patients with serious adverse events.

MR JUSTICE BURTON: Can you show me the 38? I can see the 42. Where's the 38?

A. We have to go back to ... (Pause).

MR JUSTICE BURTON: The only 38 I can see is on the top left-hand corner of page 2245, but that's limited to one

of the three groups.

MR NASH: There is a 38 as a total figure in the top right-hand column of 2244:

"Patients with at least one serious adverse event."

In the "yes" part of that table, the total number of patients --

A. Is 38.

Q. -- is 38.

MR JUSTICE BURTON: Hold on, I'm missing this.

MR NASH: 2244.

MR JUSTICE BURTON: The 38 yes's for:

"Patients with at least one serious adverse event."

MR NASH: And in the "yes" part of that table -- which means they fall within the group -- total number of patients is 38 -- the total number of yes's.

MR BEAR: It's not the total number of yes's.

MR NASH: The total number of patients with the answer "yes" is 38.

MR JUSTICE BURTON: Yes, so -- again I'm not sure what relationship this has to any of the issues in this trial, but that will no doubt come out -- you're pointing out that there were 38 patients with at least one serious adverse event and death is an adverse event?

A. It's an outcome, yes.

MR JUSTICE BURTON: And yet there are 42 patients who die?

A. And that raises a red flag for me, because we have a reporting duty to the regulatory agencies in relation to that, but it also questions whether the data as was entered in the database and the way it was analysed, if there were some checks that were not optimally functioning.

MR NASH: The other annotation is "very clear" with an arrow, can you explain that?

A. My initial response to that is, wow, this dose arm, there seems to be a preponderance of medically significant serious adverse events, or adverse events.

But then I started thinking about it, because we know from the HPM database, the pharmacovigilance database that there were about 42 or so serious adverse events reported, and, again, as I stated earlier, I do accept discrepancy because of synchronicity, of cleaning and collecting data and all that, but it kind of gave me a feeling, an idea, that there may be some double counting here.

More than one event relating -- or resulting in death, and if we start doing that kind of exercise, then it becomes highly unreliable. So I have an issue with that, because if one patient in example would have, let's say, five of those medically significant events, then you would skew your data to treatment arm A, B, C

or D, and with those low patient numbers it would be relatively easy to influence the outcome that way.

Q. Can we then, just to finish the annotations, go to 2246?

A. Yes.

Q. On the right-hand side, perhaps just quickly the left-hand side which is a table headed up:

"Adverse reaction at injection site visible at day 15."

You've made an annotation there. Can you explain what that is?

A. That stands for "injection site reaction", and this was a concern, because it could have been potentially an element of unblinding the study, because in earlier studies, it was seen that injecting this material could give injection site reactions characterised by retinas and some swelling, et cetera.

But, if we look at this data, it will be very hard to unblind patients in that regard.

Q. So we don't need to be concerned with that?

A. Well, again, these are very small patient numbers, so I wouldn't hang my hat on it, but this data, as presented, does not support a notion of injection site reactions to be a core morbidity of importance.

Q. Then the right-hand column is the beginning of table 7 which is outcome measurements, and again I think for our

benefit, Dr Goedkoop, the Glasgow Coma Score is the first table, lower scores are worse.

Just explain very briefly what the Glasgow Coma Score tells us?

A. The Glasgow Coma Scale, GCS in this case, is a composite end point to characterise the condition of the patient that has some lowered state of consciousness of the brain, so it's an indirect measure describing the functioning of the brain.

Now, D3 stands for the third day, so it's basically again making the thought process, and if we look at those figures, I will leave the conclusion open, but there were two elements for me, one being that looking on efficacy in such small numbers is not very useful.

Q. Can you explain that a little bit further, Dr Goedkoop, because --

A. Well, I think one -- now we have to backtrack a bit in --

MR JUSTICE BURTON: Do we have to? Has it got anything to do with the issues in the trial?

MR NASH: It has, my Lord, yes, because --

MR JUSTICE BURTON: Yes?

A. I think --

MR BEAR: Can I put down a -- I don't want to interrupt the cross-examination, but can I say I disagree with what my

learned friend has just said.

MR JUSTICE BURTON: Yes.

MR NASH: This of course is examination-in-chief, my Lord.

Could you please, Dr Goedkoop, explain a little bit more about that?

A. Okay. I think on the onset of this trial, and the defendant being a strong proponent of that, that if you want to have successful trials in these kind of conditions, such as traumatic brain injury, but it's also for other CMS conditions, you will have to be able to power your study so you can really show superiority in a statistical fashion.

For that you need fast patient numbers, and I think a projection has already been made that if a subsequent study is to be done, assuming that this compound is safe, one would be looking at about 2,500 patients per study arm, if you want to be able to show superiority.

So it's really astounding to see that we want to draw conclusions on such small patient numbers.

Secondly, I think a more recent analysis on the Cochrane database, going for traumatic brain injury, again, shows that if you look at low patient numbers, you will not be able to draw hard conclusions in terms of efficacy.

Also, I do think that these tables as presented, the

decision that was made is purely on the safety, and not necessarily on the efficacy.

Q. Thank you, Dr Goedkoop. Then just explain, please, these annotations we have at 2246:

"GCS? D3."

A. So GCS stands for Glasgow Coma Scale, D3 for day 3 and simply a question mark, because I wanted to understand whether there are true differences here, yes or no. I can see the numerical differences, but what does that mean in statistical terms? Probably not much.

Q. Then a little further down, you've written some words there. Can you just fill those in for us, please?

A. Well, "better", it's again reflecting to: is any of these treatment arms performing better than the other? Only looking at numerical figures, and also bearing in mind that the range is quite large, if we look at the mean and then at the figures around that.

Q. Is that: what number of patients would be needed to be significant?

A. Yes, I think if one takes this data, and a statistician can do the calculation, then the question I had is: what number of patients would you really need to show a difference between any of those arms?

Q. Then I think the last page of this we need to look at is 2247, and again run through the annotations for us,

please.

A. Okay. The circle speaks for itself, because it's highlighting that there were a lot of missing data fields, and I don't know how they have used the data fields, whether there was less observation carried forward, which is a statistical methodology, it's relatively conservative, whether it was censored data and all these kind of things. GCS stands for Glasgow Coma Scale, D6 speaks for itself, day 6, and the arrow, it's of course: did the patient improve, yes/no?

Q. I'm sorry, I didn't catch that last part.

A. Did patients improve per study arm, yes/no.

Q. Right, and the downward arrow signifies?

A. Again, a circle around the number of missing values in this relation, so in my mind if you start losing, or you don't have the data available to yourself, and the denominator is being reduced, the accuracy of your outcome and the interpretation thereof will become less secure, the standard deviation will actually widen.

So GCS, Glasgow Coma Scale, D15, day 15, and 1P, that's for placebo, and that goes -- that seems to be a bit higher there.

Q. So the downward arrow signifies what, Dr Goedkoop?

A. That -- let me see the Glasgow Coma score. That they seem to fair a little bit better if you just look at the

numerical difference.

Q. The placebo group fairs better?

A. Yes.

Q. Then finally in the right-hand side of this page, again just run through it quickly with us, please.

A. Again, looking at these parameters, the two little snakes basically reflect similar, or more or less the same.

Then: what about the mean change from baseline, are groups statistically balanced? Here I tend to go a little bit deeper into these parameters, because you can report the data as it is, but one could also control for the variation at baseline, and we know from the study that the baseline Glasgow Coma Scale to what you compare is very different from patient to patient, as you would expect.

Now, one way of controlling that is taking that out, so that's by looking at the change from baseline and then calculate either the mean or the median, with its standard deviation, et cetera, and then compare that between treatment arms, and this is a very common methodology that we apply in many, many studies concerning interventive type of treatments.

Q. Thank you, Dr Goedkoop.

A. You look a bit puzzled.

Q. I'm just wondering whether that is something that we can develop or not, but I think we'll leave it there for the moment anyway.
A. Okay.
Q. And then finally, you've got a Hireos with, again an approximation sign.
A. Yes, the numerical figures look more or less the same to me.
Q. Yes. Can you now put that table away, please, for a moment at least? You may need to keep it to hand around you, but you can close it up perhaps?
MR JUSTICE BURTON: Has it come out of the chronological bundle?
MR NASH: It hasn't come out of the witness bundles.
MR JUSTICE BURTON: Let's do that. You can take those pages out of the chronological bundle and put it into the core bundle at tab 18. It's 2243 to 2248. Take them out completely and put them into the core bundle behind tab 18.
Yes?
MR NASH: Can you then return, please, Dr Goedkoop, to your statement and go to paragraph 24, and you're dealing here with your exchanges with the school in November seeking certain information --
MR JUSTICE BURTON: Can I ask you before we move on from

that, first of all, you've referred to your familiarity with the H -- I forget what they are --

A. HPM.

MR JUSTICE BURTON: HPM database, but that was unblinded -- so sorry, that was blinded, wasn't it?

A. Yes, it's simply only the last column as we saw in table 5.

MR JUSTICE BURTON: So it would be total numbers?

A. Total numbers, yes, and in principle, HPM will never be unblinded, unless there is a true safety concern again.

MR JUSTICE BURTON: Right, thank you.

Secondly, did you raise at the TSC telephone meeting the point that you've made today about the difference between 38 and 42?

A. I think I did. I mentioned that as well as the discrepancy between the HPM figure and the figure as presented to the TSC in terms of the total number of SAEs, without contesting either one being right or wrong.

MR JUSTICE BURTON: Yes, but in relation to discrepancies, that's not a matter of right or wrong; that's a matter of the fact of discrepancy, isn't it?

A. Correct.

MR JUSTICE BURTON: So what did you say about the discrepancies?

A. Well, that I gave the exact figure of the number of SAEs that were reported by HPM until that date, or the last snapshot I was aware of.

MR JUSTICE BURTON: Yes.

A. And then of course we had the figures as presented to the TSC, and I mentioned that to --

MR JUSTICE BURTON: And what did your colleagues say about that?

A. What my colleagues said? Well, I think initially the discussion was more about stopping the trial rather than about the next steps, and it's upon my request whether we could maybe consider suspension until further notice, and this may not be good English, but it's not my native language anyway, but what I truly meant is, well, do we feel confident looking over our shoulder, in time, and say: listen here, we have really taken the right decision, on the data, as it was presented today, to stop this trial.

And I think then we had quite a discussion, and I can say Mrs Shakur also confirmed that there may be an incompleteness of the database, that there is of course an ongoing cleaning and that of course some discrepancy may exist between the two.

So to me that was not surprising to be honest.

MR JUSTICE BURTON: And the 38 and 42, did anybody mention

that -- did you mention that specifically?
A. I mentioned that --
MR JUSTICE BURTON: How can there be 42 deaths and only 38 SAEs?
A. Yes, I did mention that, and the reply to that was that there were patients that had more than one serious adverse event, which is also stated in the title of that table.
MR NASH: I was going to ask you about paragraph 24 of your statement, Dr Goedkoop.
A. Yes.
Q. Particularly the last part, where you deal with the exchanges about information, and you comment:
"As mentioned above, what I had in mind was a line listing of all the SAEs [as a piece of information you wanted to get from LSHTM]."
Why was that a piece of information which you thought was important to obtain?
A. To me -- well, first of all, I think it's part of a normal review of safety, that you look in a blinded way at all the serious adverse events and any other safety concerns that are out there, and I leave causality in the middle right now, and the reason for that is -- and in particular now, having been confronted with these DSMB tables, I wanted to understand why this

decision was made.

For example, if there would have been ten patients with pneumonia, well, that would raise a red flag because then there's a preponderance of a specific adverse event, and I know from the HPM listing that it's all over the place, these are all very different kind of symptoms that are being given a preferred term in the series of database.

So there is no specific adverse event or term that stands out in this situation, which means to me that I don't have a specific concern about the safety per se.

MR JUSTICE BURTON: What's a line listing?

A. A line listing would be if the London School reports an X number of serious adverse events, that basically you get a list of what these serious adverse events are, like pneumonia or cerebral oedema, elements that are important.

Now, why is this important? Because there are adverse events that are probably related to the underlying condition, and, therefore, do not require to be reported as such.

MR NASH: Finally, Dr Goedkoop, you make a comment over the page in your statement, page 9. Within paragraph 25, you refer to Professor Roberts's statement that:

"Errors tend to reduce not magnify any negative

effects of the drugs."

You say you simply do not understand this statement. Can you explain why you find that statement difficult to understand?

A. Well, the reason I have difficulty in understanding is that you're looking at a very small sample size, and the smaller the sample size, the more an error will be outspoken.

The other risk you run is that we assume that you have a normal distribution of events over the various treatment arms, but we don't know that in this study.

What that means is that you can easily have certain -- or adverse events, or any other event, occur with a preponderance in a particular dose arm, and that would really skew your data, and it could lead you to the wrong conclusion of that data.

So that's where I do disagree with Professor Roberts, I do respect that, yes, if you have a completely normal distribution of events, then most likely the randomisation should take care of it. But what I don't know is, with the data collection and the status of the data collection, per treatment arm, the amount of data cleaned, et cetera, et cetera, per treatment arm, whether this is all balanced so to speak.

So it's really more a technical issue.

MR NASH: Thank you, Dr Goedkoop. Would you wait there, please?

MR JUSTICE BURTON: Can I just ask you one question?

A. Please.

MR JUSTICE BURTON: Paragraph 29 of your statement, you refer to a proposed TSC meeting on 5th December.

A. Mm-hmm.

MR JUSTICE BURTON: Did it ever happen?

A. No.

MR JUSTICE BURTON: Why didn't it happen?

A. I think -- I'm not sure what the legal term is for it, but basically it was not authorised to conduct this meeting --

MR BEAR: It was an ex parte application on the 4th by Xytis, as a result of which Mrs Justice Gloster --

MR JUSTICE BURTON: It came to court did it, on that day, or before --

MR BEAR: No, it was notified on that day and it came to court on that day and an order was granted --

MR JUSTICE BURTON: And as a result of that the meeting didn't take place?

MR BEAR: There was an order granted prohibiting the TSC from meeting, and had it met my clients would have been held in contempt.

MR JUSTICE BURTON: I follow.

Now, there was a communication, you say, by way of a notice for that meeting, which referred to 59 SAEs. Do we have a copy of that communication in the bundle?

MR NASH: Yes, we do.

MR JUSTICE BURTON: We're going to find it in a moment, but you say that you didn't give this figure any particular attention, and you still don't know whether it's the same 59 as the 59 that were in the DMP database and which --

A. There were 94 in the DSMB database.

MR JUSTICE BURTON: Again, I'm using the wrong expressions. HPM?

A. HPM, right.

MR JUSTICE BURTON: It was 59 in the HPM database?

A. Right.

MR JUSTICE BURTON: And 94 in the DSMB database, and what you don't know is whether, in this communication, the 59 that was being referred to, was a reference to the HPM 59 or to some different 59, but I think we ought to see this so that I can understand.

A. And in particular what I did not know is whether this was an extract of the same database as presented to the DSMB or some other snapshot.

MR JUSTICE BURTON: Let's have a look at it.

MR NASH: It's in chronological bundle number 11, at

page 3290 the document begins.

MR JUSTICE BURTON: I seem to have taken it out already. And put it in the core bundle.

So 3290?

MR NASH: 3290, the trial steering committee report, Dr Goedkoop, and then I think 3291 is the relevant page, is it?

Just for the note, one sees there in the first paragraph:

"SAEs reported to date: 59."

A. Yes.

MR JUSTICE BURTON: That's what you looked at, and you noted it, but because the meeting was cancelled, you didn't turn your mind to think what it meant?

A. I think in all honesty, since Xytis had decided to terminate the contract, I did not necessarily see the TSC as an entity at all, because to me a TSC, a DSMB, is part of the methodology of conducting clinical trials, and from that perspective, if the contract is withdrawn, then I really didn't see what I had to do with it.

MR JUSTICE BURTON: No, I understand that, but did you read this document?

A. No, not to the full extent.

MR JUSTICE BURTON: So your picking up of this 59 is something you didn't pick up at the time, you've only

picked it up subsequently, is that it?
A. No, I saw that figure on that particular day.
MR JUSTICE BURTON: If you didn't read it how could you pick it up?
A. I received the documents by courier --
MR JUSTICE BURTON: But then I thought you said you didn't read it?
A. I looked at it and then I shared it with Rowland Furcha, and that's basically it, and I told Xytis, I'm not going to take any further action unless the TSC is going to take place --
MR JUSTICE BURTON: So you noted this 59 at the time --
A. Correct.
MR JUSTICE BURTON: -- but you didn't ask any questions to yourself or anybody as to whether that was a belated acceptance by the defendant that the figure of 59 was right, or whether this was some different 59?
A. No, I did not question that.
MR JUSTICE BURTON: Thank you.
MR NASH: Thank you, Dr Goedkoop. Will you wait there?
MR JUSTICE BURTON: I've already transferred this into a core bundle, but if they could be transferred, 3290 through to 3295 could be transferred, I've got them behind tab 40, just immediately after page 42.
Yes?

MR BEAR: Now, we know that on 1st November, Dr Goedkoop, you saw tables from the DSMB. You have to say "yes", I'm afraid, for the record.

A. Yes.

Q. Those were sent to you by Professor Roberts, weren't they?

A. Correct.

Q. And those tables, or the table extracts, to be precise, contained unblinded data, didn't they?

A. Correct.

Q. Now, if you could be given witness statement bundle 2, please. So this is the first statement that you made in December?

My Lord, it's tab 17 of witness statement bundle 2.

MR JUSTICE BURTON: Thank you.

MR BEAR: Could you look at page 3 and paragraph 6? I'll just read it out:

"Since the meeting on 1st November, I have safeguarded the blinding of the study and honoured the confidentiality of the TSC."

I'll move on to the next sentence:

"It was agreed within the TSC at the meeting that I was allowed to make qualitative statements to Xytis. Accordingly, I could make statements that would not

compromise the continued blinding of data which would not, in any case, be sensible or in the interests of Xytis."

So just pausing there, am I reading this correctly? What you're saying is that anything which compromised the continued blinding of data wouldn't be sensible?

A. Can I just give you an answer or you want just the yes or no or a no?

MR JUSTICE BURTON: No, no, no, he only suggested that if it was yes or no, answer yes or no, rather than nodding the head or shaking the head, just for the record, but if you want to say something other than yes or no, please say what you want.

A. Okay. No, the answer to that is: yes, it is important to maintain blinding at any cost, unless the drug is really unsafe and there's no need to further continue the trial. I think it's to the best interests of both the sponsor as well as the CRO or the service provider to maintain that blinding, in order to allow for continuation of the trial. I think that makes all the sense in the world. So the answer is "yes".

MR BEAR: And referring to the continuation of the trial, if we drop down about six or seven lines from the sentence I just took you to, can you see a line beginning with the word "studies", about seven lines down? So the

first word on the line is "studies".
A. I'm not seeing it immediately, but --
Q. That's all right, take your time.
MR JUSTICE BURTON: It's eight lines from the bottom. Your finger is too high up, keep going.
A. Okay.
MR JUSTICE BURTON: The word "studies" is the first word in the line.
A. Maybe you can point it out. I don't immediately see it. Yes?
MR BEAR: Do sit down if it makes you nearer the document and easier to see. I wanted to draw your attention to this sentence:
"I am more than aware that only by maintaining the blinding a study may be restarted."
So, again, have I read it correctly, if I read it in this way, that if you don't maintain the blinding, you won't be able to restart the study?
A. The answer to that is yes and no. The immediate answer --
Q. Sorry, I will give you a chance to come back, but I just wanted to know -- my question was actually what you meant or what you appeared to mean in this sentence. So can we agree that what you're saying in this sentence that I read out to you was that unless the blinding was

maintained, the study couldn't be restarted. That's what you wrote.

A. Well, I'm going to deviate from what you want to hear. The answer is both yes and no, if you allow me.

MR JUSTICE BURTON: Yes, go on.

A. The immediate response is "yes", but you always have the opportunity to amend a protocol and it means that the blinding itself is part of the methodology. You could consider at some point in time, now that we're heading for this further interim analysis of data, to break open the study and make it an open label study as they call it, so without a placebo control, and hence an issue of blinding.

So you always have that opportunity to amend a protocol if need be.

MR BEAR: So that would be making the study unblinded completely?

A. A different methodology, correct.

Q. If you wanted to maintain it as a double blind study --

A. Then the answer is "yes" to your question.

Q. What you say in paragraph 6, just looking at the first few lines again, having referred to the TSC meeting and having referred to the exception which you say was there for you to make qualitative statements, you go on to tell us that you couldn't go any further than that

because it would compromise the blinding. Is that right?

A. Yes, I think I could only give qualitative statements and overall data which summarises the four treatment arms.

Q. So if, for example, you had shown Mr Simmon the tables that had come from the DSMB, would that have compromised the blinding?

A. Correct.

Q. Would that have then prevented the study being restarted unless it was made an open study?

A. Not necessarily, but I think that any moment you breach that blinding and you share it with more people, I think you get more and more in the situation, where people may be biased that are directly or indirectly involved in the conduct of the study.

Q. Mr Simmon is the direct superior of Mr Furcha, isn't he?

A. Correct.

Q. And Mr Furcha is the project manager for the trial?

A. Correct, yes.

Q. And he has direct contact with all the CRAs doesn't he?

A. Also correct.

Q. So Mr Simmon is plainly involved, at one remove, in the conduct of the trial, isn't he?

A. Correct, yes.

Q. What I suggest is that your own evidence in paragraph 6 indicates that by Mr Simmon looking at the tables which came from the DSMB, the study now may not be restarted?
A. We are in a court setting, am I correct? And I think only under that notion Vince has been unblinded.
I think you had a discussion yesterday about that, where both parties agreed on it. So I really don't see what you're trying to get --
MR JUSTICE BURTON: You're not being asked about what's happening now. I know it's difficult, you are trying to think one ahead, why is he asking these questions?
A. Of course, yes.
MR JUSTICE BURTON: But I think you're being asked about -- or it's going to be suggested to you that you breached the obligation before the start of the hearing, that is before yesterday.
A. Then you should ask me --
MR JUSTICE BURTON: That's what you're going to be asked about. So would you agree that what you say here would mean that you shouldn't discuss the unblinded data with Dr Simmon, at least outside a courtroom?
A. Correct.
MR BEAR: I am going to ask that, but I'm actually on a slightly different point here. Let me put it this way: if Xytis were unable to restart this study -- the

BRAIN Trial -- then obviously the BRAIN Trial would never reach a conclusion, would it?

A. I'm not sure where you're trying to lead me, but --

Q. Don't worry about where I'm trying to lead you, just answer the question?

A. I do, because you're trying to kick in an open door. The answer to that is, yes, that's a rhetorical question in my mind.

Q. If Xytis then wanted to try to gain approval for Anatibant, the drug, it would have to restart with a completely different study, wouldn't it?

A. That's correct, or amendment of the study:

MR JUSTICE BURTON: Or a what study?

A. Amendment of the study protocol.

MR BEAR: To make it entirely open?

A. Different methodology.

Q. It's pretty standard, isn't it, for clinical trials into new interventions to be double blinded?

A. If you want to get into that discussion. I tends to disagree. If you do cancer studies, and that's about 70 per cent of all the NDAs at FDA and EMEA, you cannot do placebo control trials in most instances because placebo doesn't work in cancer. So I think we should try to stay away from that kind of generalisation --

Q. If we leave aside cancer studies.

A. -- and I will take you one step further on this one. This study was a primary end point being safety, and for safety purposes, in general, studies are not of double blind nature.

Q. I'm going to suggest that the evidence you've just given is completely false, and that you know perfectly well that a study of this kind would be expected to be double blinded. That's correct?

A. I disagree on that one.

Q. It's a fundamental principle of clinical trials that they're operated on a double blinded basis to prevent either conscious or unconscious bias, would you agree with that?

A. You are trying to nail me on something that --

Q. Don't worry about what I'm trying to do. Just tell us if you agree or disagree with my proposition.

A. I disagree, and on the simple notion -- and if you will do a literature search, you will find there are more open studies when you are in the early stage of clinical development of any of these products, rather than double blind and placebo control trials, and the reason for that is because it's more costly to do it that way, and first you have to establish that your drug is safe.

Q. So why did Xytis bother to do a double blind trial in this case?

A. Now you're asking me a question I cannot answer, because I was not part of that history in designing the clinical trial. It would definitely not have been my clinical design, but that's another discussion.
Q. Did you record your views at any point after coming on board with Xytis?
A. Yes. We have discussed that in the corridor, but it is not my business to look back over my shoulder on what has been done, but it's to deal with what is ahead of us.
Q. You attended a meeting of the TSC in June, didn't you?
A. Correct.
Q. Did you mention there that you thought it was totally unnecessary for the trial to be double blinded?
A. No, because that was not a point of the agenda, and, again, I came on board once the study was already established and all the methodology around it.
Q. If Xytis started a new trial -- so not opening up this one, but started a new trial -- do you agree that none of the data that had been collected so far in the BRAIN Trial would be relevant?
A. I disagree, because safety data is reported to the authorities, hence you cannot circumvent that, and I think it is actually important, because it may well mean, if you do further analysis, that certain subsets

of patients do have more toxicity concerns than others. So I think you have to be a bit more sophisticated about this.

Q. The data that was collected up to 19th October shows that Anatibant is dangerous, doesn't it?

A. I disagree on that one.

Q. You disagree?

A. Yes.

Q. You think it shows that it's safe, do you?

A. No, that's not what I'm saying either. No, I don't know, and that's why we are going into the suspension until further notice mode and go to a full analysis of the data set, and hopefully at --

MR JUSTICE BURTON: That's the second time you've said that. What does that mean, "going to a full analysis of the databases"?

A. Until 1st~November, 227 patients were treated.

MR JUSTICE BURTON: Yes.

A. And the treatment was immediately stopped in patients that were still active on treatment.

MR JUSTICE BURTON: Yes.

A. And I think that's exactly what you need to do.

Now, this whole data set -- and we owe it to the patients, we owe it from an ethical point of view, to do a full analysis at least on the safety -- I leave the

efficacy in the middle, but really on the safety. If then the conclusion still stands, I think it's probably not worth your while to further develop this drug for this specific indication.

MR JUSTICE BURTON: Now, who's doing that?

A. Well, I think partially we are here to discuss the contract between the defendant and the claimant, and I don't know the answer to that question, because I don't know what the outcome of this meeting --

MR JUSTICE BURTON: As far as you're concerned, leaving aside the contractual dispute, you are expecting someone to do what you, ten minutes or so ago, called an interim analysis?

A. Yes, correct.

MR JUSTICE BURTON: Sit back and look at the 227 we've got at the moment, clean them all up, reconcile them and look at them, both from the efficacy point of view and the safety of view?

A. In my mind, it is Xytis, the sponsor, and then with whomever they see fit to appoint in helping them understand the data, experts, another TSC, the same TSC, I really don't have the answer to that question today.

MR JUSTICE BURTON: That's what you had in mind, was it, when you suggested at the TSC that the better course was not to stop the trial, but to suspend recruitment?

A. Correct.
MR JUSTICE BURTON: As far as you're concerned, you thought the next thing that was going to happen was that there was going to be a full analysis of the already recruited patients?
A. Yes.
MR BEAR: Just looking at the data that's been collected so far, taking it at face value -- I appreciate you say that one shouldn't -- if we take the data at face value that was collected up to 19th October, do you agree that appears to show that Anatibant is dangerous?
A. It depends to which table you look, and the data seems to be flip-flopping between the four treatment arms, and if I look at the standard deviations with that, they seem to be overlapping, so I cannot hang my hat on it. The only table that raises a red flag, and that's to your benefit, is where it talks about all the AEs in the patients and that seems to be a much lower number of patients with adverse events as compared to any of the active treatment arms.
MR JUSTICE BURTON: Can you tell me which one that is?
A. I think that's the first one in exhibit --
MR JUSTICE BURTON: Hold on, we've got it, haven't we, in the core bundle now?
MR BEAR: I'm going to be looking at this in a moment. So

shall I come to it?

MR JUSTICE BURTON: Very well, just as long as somebody reminds me which one it is that the witness is worried about.

MR BEAR: I'll do that very shortly.

So is this your evidence, that apart from that one table, you don't think that the data indicates that Anatibant is dangerous?

A. Correct.

MR BEAR: Can we then look at the table? Let's start off by looking in core bundle 2, first of all, at tab 45, which is DSMB's letter?

I want to make it quite clear to you, Dr Goedkoop, that I'm going to challenge the evidence you just gave, all right? Do you understand that?

A. Yes, yes, I'm listening.

Q. Do you have now the DSMB's letter of 1st November?

MR JUSTICE BURTON: Shall we take the transcriber's break?

MR BEAR: Yes.

MR JUSTICE BURTON: Five minutes for the transcribers and perhaps while that's being done you can reconnect me? Thank you very much.

(12.05 pm)

(A short break)

(12.10 pm)

MR BEAR: So Dr Goedkoop, we were looking at tab 45, please, and you got this letter on 1st November, didn't you?
A. Correct.
Q. Thank you. If you look at point (b), it says that the efficacy results at day 15 provided no evidence of benefits and there were adverse trends in all three outcome measures. Do you see that?
A. Yes.
Q. What I suggest is that what that means -- just taking it at face value, all right -- is that so far from reducing neurological impairment in subjects with TBI, Anatibant tends to increase the degree of neurological impairment. That's correct, isn't it?
A. I don't know, because the data as presented is reflecting numerical changes, but not a change from baseline in these patients, so I cannot just draw that conclusion from it.
Q. That's what the DSMB are saying, isn't it?
A. What they're saying I don't really care about. It's the data that was presented. I am not contesting the DSMB's recommendation. What I am contesting, or what I'm looking at, is the data as presented to me, and you're asking for my interpretation of it.
Q. I was just asking you in the first place what the DSMB meant. Can I ask you again: do you agree that just

looking at what they wrote here, the meaning of what they wrote is that Anatibant increases the degree of neurological impairment?

A. Yes.

Q. And that is because, in a nutshell, the outcome measures are all different scales which indirectly record the degree of neurological impairment?

A. Correct.

Q. So if you score worse, as a subject, on any of those scales, you are in a less good condition?

A. If you look at the Glasgow Coma Scale, I would tend to agree. If we look at another scale, like the Hireos, et cetera, then I don't think that's a valid data tool, but I will leave the value of that in the middle, and not only that, if you look at the individual treatment arms, you will see that some of those values, numerical values, are flip-flopping between the different treatment arms.

So it is very hard to see what the consistency is of that data.

Q. I'm sorry, I wasn't asking you about the statistical analysis done by the DSMB, but just about the general principle that, on any of these scales, if you have a worse score than somebody else, you are neurologically worse off than that other person. That's correct, isn't

it?

A. As a treatment effect it will still depend where you came from in terms of your baseline, because you're not recruiting a homogeneous population of patients with the same or similar baseline.

Q. I'm going to put the question again. If you score worse on any of these scales, are you in a less good condition than someone who scores better?

A. Yes.

Q. So adverse trends, if we look at what the DSMB wrote, adverse trends in all three outcome measures equals people being worse off, doesn't it, medically worse off?

A. To me it means that there is no proof. Or that at this stage of the analysis, on what the DSMB has seen, that there is no hint of efficacy, but it's not excluding it.

Q. No, but I'm looking at the second part of (b), please:

"... there were adverse trends ..."

Do you see it says "and":

"... and there were adverse trends in all three outcome measures."

A. Yes, I see that, but it doesn't tell me whether that was with placebo or with the active treatment arms, was it both -- in both groups in that regard, could be one improving less than the other, or worsening more than the other.

Q. It doesn't tell you if it's as between placebo and active treatment arms?
A. No.
Q. Why would the DSMB mention this unless they were drawing a comparison between placebo and active treatment arms?
A. Because -- and that's where we get to the tables -- because the data is indeed that the treatment arms show somewhat less improvement than the placebo arm.
Q. Does it appear from this and the tables that it was the DSMB's view that on the data collected up to 19th October, the drug was associated with people having a higher degree of neurological impairment than placebo?
A. Not to me. As I mentioned before, we are not dealing with the same baseline, and I think we can have a very semantic discussion here.
Q. I'm just asking you about what it appears the DSMB concluded.
A. The DSMB drew its conclusion and I think they come with a recommendation to TSC and then the TSC -- by the way I am a non-voting member there -- but then it's up to the TSC to make a decision on the further conduct of the study. So my interpretation of the limited data provided is maybe not directly the same as that of the DSMB.
Q. No, I was just asking you whether it appeared that the

DSMB's view was that the drug was associated with people having a higher degree of neurological impairment than people who were just on placebo.

A. I'm still a bit confused why you are asking me that question. You should ask it to the DSMB.

MR JUSTICE BURTON: No. You received this letter, and it's a question of what you understood from this letter.

A. What I understood is that there is a recommendation of the DSMB to think of stopping the study.

MR JUSTICE BURTON: Yes, but in relation to little (b) -- the reason for their recommendation as set out in (b) --

A. Yes.

MR JUSTICE BURTON: -- now you're being asked about your understanding of what that meant.

A. The way I read it is that they have a concern about efficacy of the treatment.

MR JUSTICE BURTON: Yes:

"... because there were adverse trends in all three outcome measures."

You're being asked what you understand by that.

A. What I understand about that is that they think there was a worsening, or less improvement than expected or as compared to probably the comparator arm being the placebo.

MR BEAR: Thank you. Now, in any clinical trial, the

protocol specifies the methodology to be followed, doesn't it?

A. Correct.

Q. That would include the information to be collected?

A. Correct.

Q. And, in any clinical trial, the case report form, the CRF, is the key source of data on patients in the study, isn't it?

A. Correct, yes.

Q. A clinical trial can only be continued if throughout the trial there is a positive outcome that can be anticipated as between the risks of the trial and the rewards of the trial. Is that correct?

A. Again, that depends on the methodology, because not all studies are designed having a DSMB, trial steering committee, interim safety monitoring, et cetera, et cetera, so --

Q. Can you look at tab 48 in this bundle, please? You should have there ICH-GCP.

A. Yes.

Q. Are you familiar with that?

A. Yes.

Q. I'm looking at the numbers stamped at the very bottom. Could you look at page 96?

A. Yes.

Q. Section 2:

"The principles of ICH-GCP."

Can we look at the last sentence of section 2.2:

"A trial should be initiated and continued only if the anticipated benefits justify the risks."

A. Correct.

Q. That's obviously correct, isn't it?

A. Yes.

Q. So on the basis of the DSMB's conclusion in (b) that we were just looking at, the trial would have had to have been suspended, patient recruitment in the trial would have had to have been suspended, simply on the grounds of what they said in (b). Do you agree?

A. It's what they recommended, yes.

Q. No, but simply on the grounds of (b)?

A. Yes, but, again, I've said that before, I'm not contesting the DSMB's decision.

Q. Is it also right to say that unless the full data on the 227 patients, which is obviously more than they were looking at -- I see you nod -- unless the full data on the 227 patients changes something from the 140 which the DSMB looked at, Xytis will not be able to restart the trial, will they?

A. That's correct, and one shouldn't, because then it means there is a safety concern or an efficacy concern, or

both.
Q. Under the CTSA -- you know what I mean by the CTSA, do you?
A. Yes.
Q. -- there would then be publication of that result, wouldn't there, if the CTSA was still in force?
A. Yes, correct.
Q. And indeed, LSHTM can continue to publish in any event, can't it?
A. Not without the consent of the sponsor.
Q. With consent and so on, I'm just getting the general point across.

If there was publication of the result, that there were the problems that we see summarised by the DSMB, that would make it very difficult to get any investor to fund any other trial into Anatibant, wouldn't it?
A. I would think so, yes.
Q. All right. Now can we go back in core bundle 2 to tab 18, please? What I want to look at is the document which was originally in tab 18 which looks -- starts off like this, Dr Goedkoop. (Indicates). It should be in the same bundle that you were looking at, divider 18.

In your evidence-in-chief we looked at your copy, but this is slightly easier to read.
MR JUSTICE BURTON: Can you just, before you start to answer

my question of a few moments ago, which was the one table which you told me caused the red flag?

A. That's the table --

MR JUSTICE BURTON: Just in here, which one? Just show me which page it's on.

A. It's the table on page 2762, the top one. So that's the relation to study drug.

MR JUSTICE BURTON: That's the one serious -- that's the one against which you put your comment -- can we give this a table number? It doesn't have a table number already, does it?

MR BEAR: No, they're all sub-tables. Am I right, Dr Goedkoop, does it start at the bottom of 2761?

A. Correct, that's where it starts.

Q. That's where the heading is?

A. Yes.

Q. And is always the way the heading has become separated from the data.

MR JUSTICE BURTON: And it's the one which starts at the bottom of page 2244, is that right?

MR BEAR: This is now looking at Dr Goedkoop's copy?

MR JUSTICE BURTON: Yes, and so it's the one against which you put the comment at page 2245 -- just keep going in that bundle --

A. 2245?

MR JUSTICE BURTON: Yes, is that the one where you put the comment at the top?

A. Correct.

MR JUSTICE BURTON: Thank you. That's the one I'm going to call the red flag table. Thank you. Yes?

MR BEAR: Now, let's look at the first table, please, in the document at 2761.

Do you see that? It's:

"Patients with at least one serious adverse event."

A. Yes.

Q. If you could keep a finger in that table and go either forward or back, depending on where it is, to your own document, to 2244, you had the marking 101 there, didn't you?

A. On the left-hand side, yes.

Q. I think earlier today, you told his Lordship that that was the number of adverse events, is that right? Is that what you said?

A. Yes, number of adverse events per patient in the active treatment arms combined.

Q. 101 can't be the number of adverse events per patient, can it?

A. Well, in another trial, maybe.

Q. In this one?

A. No. No, no, no.

Q. What is 101, Dr Goedkoop?
A. That's the total number of adverse events as you see in the table underneath, all doses of XY2405 combined.
Q. Can you --
A. So that's page 2244 --
MR JUSTICE BURTON: On 2761, which is what you were inviting the witness to look at, is that right?
MR BEAR: Yes, which is the same --
MR JUSTICE BURTON: It's the second table down:
"All doses combined."
MR BEAR: Yes.
MR JUSTICE BURTON: That's the 101 that he says it's referring to.
A. Corrects.
MR JUSTICE BURTON: It's the total number of patients with at least one serious adverse event in the three treatment groups.
MR BEAR: That's right. So in fact it's the total number of patients, isn't it, who qualify for this table?
A. It's the number -- yes.
Q. It's not the number of adverse events at all, is it?
A. Let me see. Just a sec, please. (Pause).
So it's the number of patients with an adverse event.
Q. With at least one?

A. With at least one, yes.
Q. That's actually quite easy to see, isn't it, because each of the three treatment groups has a total number at the bottom of the first part of the table, doesn't it, which is 31, 32 and 38?
A. Yes.
Q. It's obvious, when you look at it, that this isn't recording the number of events; it's recording the number of patients who meet a certain criteria?
A. Yes.
Q. Correct?
MR JUSTICE BURTON: And it's a total of yes's and no's.
MR BEAR: Yes, it's the total population out of which we then look at the proportion, correct?
A. Yes.
MR JUSTICE BURTON: So it's not -- it's neither the total number of adverse events, nor the total number of patients with adverse events, is it? Because it's a total of the yes's and the no's?
A. It's the number of patients that were in the three treatment arms, combined.
MR JUSTICE BURTON: Yes, but it's not the total of those with the serious adverse event. For that, you have to total the yes's.
A. Correct.

MR JUSTICE BURTON: Which is 34.
A. So this is the denominator, so to speak.
MR JUSTICE BURTON: Yes.
MR BEAR: Yes, this is the pool, isn't it?
A. In the number of patients that had active treatment, correct.
Q. And also the number who had placebo, we can see the same --
A. That's next to it, yes.
Q. Yes, and if we look at the figure in the bottom right of the main section of the table, we get 140, don't we?
A. Yes.
Q. And 140 is the number of patients who are in this database?
A. In the database, yes.
Q. Yes. Now what I suggest we compare here is, first of all, the percentage for the placebo group. Can you look at that?
A. Yes.
Q. That's 10.26 per cent, isn't it?
A. Are we looking at the same table?
MR JUSTICE BURTON: It's in the column -- the first table, second line down after "yes", "4 placebo, 10.26 per cent."
A. I see that, yes, 10.26.

MR BEAR: That means that 10 per cent of the placebo group have at least one serious adverse event?
A. Correct, yes.
Q. What's the corresponding figure for the combined treatment group?
A. The -- so that's the other ones.
MR JUSTICE BURTON: It's fairly easy. It's 34, isn't it, and there's 101 of them, so it's approximately 34 per cent, is that right?
MR BEAR: Yes, well we can get it exactly because there's a percentage in the little bit of the table underneath:
"All doses XY2405 combined. Has serious SAE: yes. Frequency: 34. Per cent: 33.66."
Yes?
A. Yes.
Q. That's what we compare with the 10.26, isn't it?
A. Yes.
Q. That is a pretty big difference, isn't it?
A. If you do the statistics -- and I don't think you -- I was presented the data as it is. I did not have the means to do a statistical calculation --
MR JUSTICE BURTON: Isn't this a red flag, Mr Goedkoop?
A. Yes, but I think you can see on my annotation that P, with the arrow next to it, seems to be faring better and that's on page -- what is it -- 3474 -- seems to have

less of a safety concern.

MR JUSTICE BURTON: I'm sorry, I'm missing here, P with the arrow next to it, is that opposite this table?

MR BEAR: Yes, the witness is referring to the top right-hand table on 2244, I believe.

MR JUSTICE BURTON: Yes.

MR BEAR: Is that right, Dr Goedkoop?

A. Yes.

MR JUSTICE BURTON: Is that in relation to this --

A. The scriptogram for me means that I thought that the placebo may be better off than the active.

MR BEAR: This is a serious red flag, isn't it?

A. Yes, because of course we have to be concerned about safety.

Q. What was the primary analysis which the DSMB was supposed to carry out, Dr Goedkoop?

A. What do you mean by the question?

Q. Do you not understand the question?

A. No, I don't.

Q. You say in your witness statement that when you joined Xytis, you familiarised yourself with the protocol on other trial documents?

A. Correct.

Q. Is that correct?

A. Yes.

Q. What about the DSMB charter, is that a trial document?
A. Yes, that's a trial document.
Q. So are you familiar with the DSMB charter?
A. Superficially, yes.
Q. Superficially familiar?
A. Superficially, yes. I skimmed through it and that's it.
Q. You skimmed through it, and that's it?
A. Yes.
Q. Do you want to take core bundle 1?
MR JUSTICE BURTON: Tab 6.
MR BEAR: Tab 6. Do you think it was adequate for you just to skim through it, Dr Goedkoop? Do you think it was adequate for you just to skim through it?
A. Yes, because again this was a pre-established part of the methodology in the conduct of this clinical trial. I had no say in that.
Q. It was up to you how much you read and what you read, wasn't it?
A. Yes.
Q. Wouldn't a doctor sitting on a trial steering committee be expected to be fully familiar, not just superficially familiar, with the DSMB charter?
A. Yes and no.
Personally, I wouldn't, and for one reason, because the TSC and sitting on the steering committee as

a non-voting member I have no say in the whole story, and from that perspective, with pre-established methodology of the trial, I didn't feel that it was necessary to really go in a lot of detail in reading this charter of the DSMB. I've only seen what was in the protocol.

Q. You're not an employee of Xytis, are you?

A. No.

Q. You're a consultant?

A. Correct.

Q. And you offer services to a number of different companies?

A. Correct.

Q. Would it be fair to describe you -- and tell me if you don't understand the terminology -- as offering a brass plate service?

A. What's that?

Q. It's a metaphor, a figure of speech. A professional person has a brass plate on the door, which in your case would say "Dr Goedkoop" and you offer the benefit of your medical certificate and the companies concerned can then say: we've got a qualified doctor who is fulfilling such and such a role. Is that a reasonable description of the service you offer?

A. I think my services go beyond that. I think it's written

in the witness statement. I am focused on the strategic, clinical development of biotechnology products. It means I don't necessarily deal with all the day-to-day issues.

Q. By strategic, do you mean business?

A. Both business as well as the scientific rationale, all the way from the pre-clinical setting into the pre-launch phase of a product.

Q. You mean high level, do you, by strategic?

A. No, not only high level. I do a lot of ploughing through literature and designing protocols and these kind of things, so I do part of that foot work.

Q. Let's look at page 1391 in tab 6, please.

MR JUSTICE BURTON: The question Mr Bear asked you, just so we can do the setting, is:

"What was the primary analysis which the DSMB was supposed to carry out, Dr Goedkoop?"

You said:

"What do you mean by the question?

"Question: Do you not understand the question?

"Answer: No, I don't."

A. Okay, I can answer it, if you like. In my mind, a data safety monitoring board is to ensure that a study and the treatment or the procedures that you're investigated are managed from a safety point of view.

If there are any safety concerns, it's them, as an independent institution --

MR JUSTICE BURTON: Primary analysis, not primary purpose?

A. Excuse me?

MR JUSTICE BURTON: The primary analysis?

A. Yes.

MR JUSTICE BURTON: Not the primary purpose?

A. Yes.

MR JUSTICE BURTON: And you were asked what was the primary analysis that they were supposed to carry out?

A. Safety.

MR BEAR: No, I think the question that I'm trying to put is at a more specific methodological level, all right? The task of the DSMB is safety, we all know that. I'm asking you: what is the analytical tool, which was the primary analytical tool, which they were to use in the performance of that function?

A. That's an analysis of a database.

Q. No, specifically what analysis, what data?

A. Well, the shell tables, and I think you have a copy of that, were available, so it means that all the elements that we have seen in the two tables that we are discussing today, and an X number of other tables, that's exactly what you analyse.

Q. You don't really understand my question, do you?

A. Well, I'm not sure if you understand what I'm saying.
MR JUSTICE BURTON: Well, let's go to the document.
MR BEAR: Let's look at 1391. Can you see above paragraph 9 a section of indented text, tab 6.
MR JUSTICE BURTON: This is the charter, so that you know what it is, let's just go to the -- let's look first at 1384, the data and safety monitoring board charter. All right?
A. Yes.
MR JUSTICE BURTON: And then there's the introduction, the roles and responsibilities, and you're being taken through to the last page, 1391, which is part of the -- under the heading "decision making" which starts at 1380.

1391, yes? I'm not sure you're on the right page, 1391.
A. Yes. Indented text, yes.
MR JUSTICE BURTON: It doesn't look right to me, I'm not right on top of you.
MR BEAR: His Lordship is looking puzzled as to whether you --
A. I'm looking at section 8.
MR JUSTICE BURTON: Turn over another page. There it is, that's it.
MR BEAR: Thank you very much. In the middle of the page,

you should have an indented paragraph beginning:

"For the main ..."

Are we on the same paragraph?

You're nodding your head:

"For the main statistical analysis, the three XY2405 treatment groups: high, medium and low dose, will be combined and compared with the placebo group."

Pausing there, what that means is you add up all of the three dose groups, and you compare them as one with the placebo group, correct?

A. Yes.

Q. Then look at the next sentence:

"The primary analysis will compare the proportions of patients with one or more SAEs."

Pause there.

A. Correct.

Q. Do you understand that sentence?

A. Yes.

Q. Now, if you could look, without putting that away, at the tables, at the page we were on in tab 18 --

MR JUSTICE BURTON: Just so you're with us, Dr Goedkoop, that was the question which Mr Bear asked you before:

"What was the primary analysis that the DSMB was required to carry out?"

That was when you said you didn't understand the

question.

Now he's shown you where that came from. All right?

MR BEAR: Now look at -- are you on the page that says 2761?

A. Yes.

Q. At the top, it says:

"Patients with at least one serious adverse event", doesn't it?

A. Yes.

Q. So this table, I suggest, is the primary analysis that is mentioned in the DSMB charter?

A. Yes.

Q. Is that right?

A. Yes.

Q. So when we see a difference of 33.66 per cent having at least one serious adverse event in the combined treatment group against 10.26 in the placebo group, that is, in fact, the most important red flag that the primary analysis could ever show, isn't it?

A. Yes, but I don't think I've been contesting that parameter one way or another.

Q. You said earlier to his Lordship that the table you thought was important was the one that starts at the bottom of this page.

MR JUSTICE BURTON: You told me it was the only red flag, the one at the bottom of the page.

A. Okay, in that case, I stand to be corrected. It's clear that there is a safety concern. That's what we're talking about. But at the same time -- and that's why I raised the red flag -- I don't see immediately what the causality is between study drug and this table.

MR BEAR: That's the purpose of carrying out a clinical trial, isn't it, Dr Goedkoop, to see if there are patterns in the data from which causality can be inferred.

A. Absolutely.

MR BEAR: Do you agree, "inferred"?

A. Absolutely.

Q. Do you understand the word "inferred"?

A. I think I do, yes.

Q. If we note over a number of subjects a preponderance of events of one class happening to a particular class of subjects, we can infer a causal association, can't we?

A. You may be able to do so. The only element is: why weren't those serious adverse events not reported to be attributable to study drug? In the end, as you already referred to, the CRF is what the investigator supplies you with and that is to be respected.

Q. An investigator dealing with subjects who have TBI will expect to see a fair few adverse events, won't he?

A. Absolutely.

Q. It follows from the nature of the condition?
A. Correct.
Q. And some of those -- for example stroke or cardiac arrest -- could quite easily happen to any patient with TBI, couldn't they?
A. Correct.
Q. But a new drug might -- we don't know, but it might make them more likely to happen, mightn't it?
A. Yes.
Q. You agree?
A. Yes.
Q. A doctor at a hospital looking at an individual case will have no way of knowing if this kind of adverse event is related to the drug or not, will he? Do you agree?
A. To a certain extent, I agree to that, yes.
Q. The only way to test it is to look at the patterns of overall events in numbers of subjects. I see you nodding?
A. Yes, and this is exactly why you have to look at serious adverse line listings and see what the underlying conditions are.
Q. You say you have to look at what the underlying conditions are. The DSMB charter says that the primary analysis is simply to compare the proportions of

patients with at least one SAE. It doesn't distinguish, does it, between types of SAE or types of underlying condition, do you agree that it doesn't distinguish?

A. The word primary --

Q. Do you agree that it doesn't distinguish between types of event?

A. I think you could let me finish.

Q. I'd like you to answer yes or no.

A. The primary analysis -- the word "primary" also indicates that there are other end points to look upon, and I think we have to be a bit more sophisticated than just hanging your hat on one primary end point.

Q. Do you agree that the primary analysis as worded in the charter makes no distinction between underlying conditions or types of SAE?

A. Correct.

Q. So your complaint really seems to be with the methodology in the DSMB charter, doesn't it?

A. If you put it in that way, yes.

Q. I'm saying that's the way you're putting it, isn't it?

A. I don't think so, if I may.

Q. Are you familiar with the type of allegations Xytis is making in these legal proceedings?

A. Yes, to a certain extent.

Q. Are you aware that Xytis doesn't criticise the work of

the DSMB?

A. I'm not criticising it either.

Q. You're criticising the methodology, aren't you?

A. What I'm coming to -- and it's what I said before -- I am presented with a bunch of data on 1st November and I am entitled to have my own thoughts about it and see how to interpret the data. I think this is part of being scientifically active, and to try and understand the data, and that's exactly what I've done, and that's also what I'm representing.

Q. Do you agree that when we look at these tables, it's obvious that the information in them can only come from CRFs?

A. Correct.

Q. In your witness statement, you give an account, don't you, of your immediate impressions that there was something wrong with the data?

A. I had that immediate knee-jerk reflex based on the number of SAEs reported.

Q. In summary, what you say is that you made criticisms of the data at the TSC telephone meeting on 1st November, is that right?

A. I made some remarks, yes.

Q. Did you make criticisms?

A. Remarks, yes.

Q. I'm asking whether you would accept that they were criticisms or not?
A. Call it criticism.
Q. I wasn't there, so you tell me what you think what a fair noun would be?
A. I thought we were having a discussion amongst professionals and hence the observations I've made I've worded them to my best knowledge, and I have expressed them to the people in that group, and if you want to call it criticism, then add the word "positive" criticism.
Q. According to your account you were the one who convinced the TSC to suspend patient recruitment rather than terminate the trial altogether. Is that your evidence?
A. What I meant with that statement is that indeed I proposed the wording of "suspension until further notice", but, again, I'm a non-voting member, and what that means is that the people that were attending this meeting have come to a consensus of doing so.
Q. The question I asked was whether your evidence is that you were the one who convinced the TSC to take the course of suspending patient recruitment rather than the course of terminating the trial altogether. Is that your evidence?
A. And my response to that is that the members of the TSC,

the voting members, took that decision themselves.
Q. Were you the one who convinced them not to terminate the trial, Dr Goedkoop? Either you were or you weren't?
A. Well, I think you should ask that to the members that were in the TSC, because I don't know whether I convinced anyone.
MR JUSTICE BURTON: Were you the person who proposed -- whether you managed to convince them or not may be a different matter. Was it you who said --
A. Yes, I proposed.
MR JUSTICE BURTON: -- please do not terminate the trial, please only suspend it, or never mind the "please", my vote, if I had a vote, would be for suspending the recruitment, not terminating the trial?
A. Correct.
MR JUSTICE BURTON: You said that, did you?
A. Correct, yes.
MR JUSTICE BURTON: They seemed to think that was -- did they react to that when you said it?
A. Yes, there was a discussion in -- on the phone line, and so I think they considered the element that I put on the table.
MR JUSTICE BURTON: Did you have an understanding before you expressed that view as to what the views were of the other people on the other end of the phone?

A. No.
MR BEAR: So it's not your evidence, then, that the view from LSHTM, the starting point was to stop the trial altogether?
A. Well, if I go back to the opening remarks by the chairman -- and I don't want to be personal about this -- but the word "termination" was clearly used, and termination, in my limited knowledge of English, really means that you stop the process that you were active on.
MR JUSTICE BURTON: So Professor Roberts said termination?
A. Yes, he used that word.
MR JUSTICE BURTON: Did any of the others express that view?
A. Yes, Professor Sampaio from Portugal immediately supported that notion that the study should be stopped, and that it would have no chance of restarting anyway, and personally I felt those conclusions were a little bit premature.
MR BEAR: The witnesses from LSHTM don't agree with your account. Are you aware that they don't agree? Have you seen witness statements?
A. Yes.
Q. So I'm going to have to take you through that in a little bit of detail.
First of all, let's deal with the remarks, or criticisms, or whatever we want to call them. Is it

fair to say that we don't see those noted on your marked-up copy of the DSMB table extracts?

A. We're talking about a BRAIN Trial here. What you're seeing is just a small reflection of what it is that I may have thought about the tables and the information provided. So I'm not sure what your question is.

Q. My question is: is it fair to say we don't see your doubts marked up on the table extracts?

A. No, nor do I see annotations on anyone's. I'm not sure what you're trying to ask me.

Q. Don't you worry about what I'm trying to ask you. You just answer the questions. You're here as a witness not as an advocate, you just have to answer the questions.

Do you think that it is surprising that if you had doubts, they didn't find their way on to your own notes?

A. Can you repeat the question again?

Q. Yes. Do you think it's surprising that if you had all these doubts, they did not find their way on to your own notes that you made at the time?

A. And by "doubts" you mean that I do not trust the data or --

Q. Yes, the remarks.

A. The remarks? No, these were really my first knee-jerk reflex, what I thought -- if I were to be presented this data, what does it mean, what decision would you go to.

MR JUSTICE BURTON: You call them positive criticisms, is that right?

A. Yes, so, okay --

MR JUSTICE BURTON: Did the positive criticisms that you have expressed have any relationship to any of the tables that we've seen?

A. I do think so. I recognise --

MR JUSTICE BURTON: What were they?

A. I recognise that there is a safety concern. However, there is a disconnect between the SAE frequency as reported by HPM and that presented to -- in the DSMB table. I have difficulty with serious adverse events that are not related to study drug, and -- yes, these are the two predominant --

MR JUSTICE BURTON: Particularly the second one, Mr Bear is asking you, do you think it's surprising -- or why is it the case, that at least in relation to the second one there is not any kind of note on -- or is there -- on your copy with a question mark somewhere against the accuracy of the figures?

A. Because I did not put all my thoughts on paper. I'm not sure what, where this is going.

MR BEAR: If we look at the core bundle again, tab 22 --

MR JUSTICE BURTON: Sorry to interrupt, your second point was:

"I have difficulty with serious adverse events that are not related to study drug ..."

You might perhaps have put a question mark against the words in the -- at page 2761:

"... which is suspected to be related to study drug", if you had a query about that.

A. Okay, but I made that remark further down in the table where we have the category -- all the different categories of these serious adverse events.

MR JUSTICE BURTON: I think that's the one I had in mind. Let's look at your --

MR BEAR: If I may, my Lord, could we look at 2244, please?

A. Okay.

Q. I'm afraid you'll have to turn the bundle round.

A. Sure.

Q. It's the top right. Can you see:

"Patients with at least ..."

Let's start here:

"Patients with at least one serious adverse event."

If you thought there was some general uncertainty about whether this was a meaningful comparison because of issues about causality, why didn't you make a note to that effect?

A. If you look at these tables, then there is a logical sequence to them, so the causality was not -- you know,

this is the primary end point, as you already kind of stipulated. You go further down, I make that remark, and then you go to the overall table of these serious adverse events, and that's where I ask the question again: what about causality?

Q. Do we see anything indicating in your notes that you thought that DSMB's recommendation was wrong for any reason, whether because they had it wrong or because the underlying data was open to doubt? Do we see anything in your notes that indicates that?

A. No, but, again, I think you're misleading, because I've said already twice that I did not contest the decision of the DSMB, and not only that, I think I supported the TSC decision as well, although I'm a non-voting member, I think that should be clear.

Q. Now, if we look at tab 22 in core bundle 2, we'll see some minutes of the trial steering committee meeting. They were prepared not by you but by Haleema Shakur. Do you have those?

A. Yes.

Q. Have you seen them? Before, I mean?

A. Yes, this I have seen, yes.

Q. Yes.

A. Tab 22 you're talking about?

Q. Yes, tab 22. Do you agree with me that there's no

indication in these minutes that you raised any remarks or positive criticisms, as you would call it, in relation to the data or the DSMB's exercise. There's no indication, is there?

A. Well, what does that tell you?

Q. I just want to you with agree with me first of all whether I'm correct?

A. It's not there, correct.

Q. Have you tried to change these minutes?

A. No.

Q. Have you written to the chair of the TSC and said: as a non-voting member of this committee, I don't think they are accurate?

A. No.

Q. Have you sat on committees before, generally --

A. Yes --

Q. -- in your life? Do you not think it's important to try to get accurate minutes?

A. I'm not an administrator in that regard, and I think the decision was really the driving factor at that moment.

MR JUSTICE BURTON: Would you just like to look at the two pages of the minutes and see whether now you think there's -- those minutes are inaccurate?

A. No, those minutes are not inaccurate, in my mind. It is about the decision and the consensus of the TSC --

MR JUSTICE BURTON: Have a read of them before you --

A. Excuse me?

MR JUSTICE BURTON: It's not just recording the decision; it's also recording what is said to have been said, or the main points of what is said to have been said. So just quietly read them to yourself and say whether you think that they are inaccurate. Of course, they don't record everything that took place.

Yes?

A. It's talking about a decision that was made and it was unanimous, both by DSMB as well as the TSC, and being a non-voting member, I'm not necessarily part of that decision.

MR JUSTICE BURTON: The minutes so far as you're concerned are not inaccurate?

A. No.

MR JUSTICE BURTON: Thank you.

MR BEAR: Then if we turn on to the next page we've got a letter that you wrote on 2nd November?

A. Yes.

Q. In fact, it was basically Mr Simmon's draft wording, wasn't it, which you adopted?

A. Yes, we worked together on this.

Q. He sent you a draft, which you more or less adopted, that's correct, isn't it?

A. Yes.
Q. Can you say "yes" for the record?
A. Yes.
Q. Thank you. And would you just cast your eye over that letter to remind yourself of it? (Pause).
Is it fair to say that in that letter there is no reference to any criticisms that you had of the exercise of the DSMB or the TSC?
A. No, the decision was made.
Q. But is it fair to say that there's no reference in the letter to any criticisms?
A. Yes.
Q. If you had had criticisms, would it not have been natural to express them the day after in this letter?
A. To me, that would have been mustard after the meal. I think the TSC had taken the right decision and I think they have listened to my remarks, and if you have listened well the wording has changed from "termination" to "suspension until further notice".
Q. You see in your witness statement, you say that your immediate impression of the data when you saw it on 1st November was that something wasn't right, and you say you were astounded by the DSMB's recommendation. Don't you think it would have been natural to record those concerns in this letter?

A. No, because I think the objective was slightly different. We wanted to understand what that data was and what the decision was based upon. It doesn't make sense to put salt on the snails from where I stand. I'm in a prospective mode, not in a retrospective mode.
Q. In your witness statement, you exhibit quite a lot of correspondence and papers, don't you?
A. Yes.
Q. And you comment on correspondence and papers in your witness statement, correct? Generally?
A. Yes.
Q. One thing you don't refer to is an email that Mr Simmon sent on 1st November immediately after he had spoken to you. That's correct, isn't it, you don't comment on that?
A. Yes.
Q. Do you know the email I'm talking about?
A. I'll not sure which one you're -- because there were a number -- there was an abundance of emails.
Q. We'll come to it in a moment. Can we just look in your statement first of all at paragraph 23?
This is your witness statement for the trial. It's divider 2 in witness bundle 1.
A. Okay, yes.
Q. Following the meeting you spoke with Mr Simmon and then

subsequently with the board of directors:

"While given my confidentiality obligations I could not provide a copy of [what you call] the shell table extracts which I had, I did inform them of my concerns about the quality of the data and there are significant discrepancies between the data given to the DSMB and the HPM information."

Just pausing there, if that was a concern you expressed at the time to Xytis, why didn't you put it in your letter to Professor Roberts on 2nd November?

A. Because it was already discussed and mentioned at the TSC meeting.

Q. So you're saying, are you, that the minutes are not accurate?

A. No, I think the minutes -- you're getting me in circles, but the minutes describe the decision that was made upon the recommendation of the DSMB.

Q. No, Dr Goedkoop, the minutes also purport -- do you understand the word "purport"?

A. Yes.

Q. -- to summarise the process of the discussion leading to the decision, don't they?

A. It doesn't really, you know. Then I think you should have the minutes where it's really stated person by person who said what. It's not there.

MR BEAR: My Lord, I don't know if that is a convenient time to break?

MR JUSTICE BURTON: Yes. Thank you very much.

Now we're not going to finish Professor Sandercock today, are we?

MR NASH: I don't think we're getting Professor Sandercock today. We're having Dr Simmon after Dr Goedkoop.

MR JUSTICE BURTON: Are we? Of course, you're quite right.

MR NASH: Professor Sandercock on Friday.

MR JUSTICE BURTON: So Dr Simmon will start and if he doesn't finish he goes into tomorrow?

MR NASH: That's correct.

MR JUSTICE BURTON: Good, thank you very much.

(1.00 pm)

(The short adjournment)

(2.00 pm)

MR JUSTICE BURTON: Yes?

MR BEAR: Straight after the TSC telephone meeting on 1st November, you spoke by telephone to Mr Simmon, didn't you?

A. Yes.

Q. Can you turn to chronological bundle 10? Or can you be given chronological bundle 10?

MR JUSTICE BURTON: Page number?

MR BEAR: 2803, please.

MR JUSTICE BURTON: I want to see whether I've transferred it. Yes, I have, it's already in my core bundle.

MR BEAR: Are you familiar with this email?

A. Yes.

Q. And you were copied in on it, weren't you? Could you say "yes" for the record?

A. Yes.

Q. Thank you. Let's go through it. It's sent to the board directors of Xytis, isn't it?

A. Correct.

Q. "Dear all, the DSMB and TSC have concluded that the BRAIN Trial should be suspended. This is not a business issue. There is an imbalance of adverse events both serious and non-serious in all three arms of the study, individually and collectively, versus placebo. The suspension versus prematurely terminating the trial is appropriate according to Rene, based on the information that was presented to TSC. The data of all enrolled patients will be analysed subsequently before any further decision regarding the conduct of the study."

Just pausing there. In this email, Mr Simmon attributes the suspension of recruitment solely to adverse events, doesn't he?

A. Correct.

Q. And that in fact is an incorrect summary of the DSMB's

recommendations, isn't it?
A. The DSMB recommendation is to stop the trial. That's the recommendation, on the basis of efficacy as well as safety.
Q. It's the (a) and the (b) that we looked at earlier, isn't it? You're right, I should have said DSMB's reasons rather than recommendation.
So he didn't accurately summarise the DSMB's reasons, did he?
A. No, if you want to hear about the efficacy, yes.
Q. Did you seek to correct this email?
A. No.
Q. Why not?
A. Because I think the preponderance of issues we thought we were seeing was really related to, again, the disconnect between the DSMB's SAE listing, the number of those, and the HPM database.
MR JUSTICE BURTON: I thought you told me that the red flag -- and then you added a second red flag --
A. Which is the relation to, yes.
MR JUSTICE BURTON: -- yes, was not on this discrepancy point at all, was it?
A. Yes, correct.
MR BEAR: When you say:
"The issues we see were relating to the disconnect,"

I wasn't talking about the issues Xytis saw. I was talking about the description of the DSMB's reasons. Do you follow the difference?

A. Yes.

Q. Why did you not correct Mr Simmon and the board of directors of Xytis about the DSMB's reasons?

A. I did explain the situation to Vince, Mr Simmon, and I think this is what he wrote, and you may want to bear with me that this is a shock to a small company, and to put your weight on every little word is a very interesting exercise, but I think the truth of the matter is that we, as a company, had to take a decision and go with the decision of the DSMB and the TSC, but we also wanted to understand what this is about, and the primary concern, as you have stipulated yourself, the primary end point of the DSMB is looking at safety, and the efficacy, I've already commented on that earlier this morning, that I do have my doubts on the interpretation of that data.

Q. Yes, but do you agree that the board members would have got an inaccurate impression of the DSMB's reasons from this email?

A. Initially, I don't think so. Secondly, you have to bear with me, there have been teleconferences and these issues were put on the table.

I think what the board really wants is that a decision is made on data, independent of that outcome, but on good data and data that we can rely upon. This is why they're investing their money, and it is -- even so that is why we're here as a company, because we believe in the trial, and if it doesn't work because the outcome is negative and the data will have to tell us the results, then that's the decision that has to be made. That is very painful. Now it's been the fault in killing of many trials in that perspective. It is as difficult as continuing a study or setting up group trials.

Q. So your concern as a company is to fully understand what is going on, is that right?

A. Absolutely.

Q. This email does not contain a full understanding of what's going on, does it?

A. No, because, again, we are talking about a moment in time. If you are confronted with something that may have a major impact, you focus first on trying to convey the key message to the members, and they will need a bit of time to absorb and react to it, and there will be ...

Q. Let's look at the next sentence:

"One member of the TSC wanted the trial halted, but LSHTM argued for suspension."

So is it fair to read this as saying that one member, who was not from LSHTM, wanted to end the trial, but LSHTM argued for suspension only, is that a fair way to read this?

A. Maybe you can repeat the way you are saying it.

Q. Yes, of course. Is it fair to read this as saying that one member of the TSC who was not from LSHTM wanted to stop the trial altogether?

A. Yes, I think (inaudible).

Q. And it was LSHTM who argued against that and in favour of suspension?

A. Yes.

MR JUSTICE BURTON: That's not what you told me earlier.

A. No, and I don't think that's how I conveyed it to Vince either, to Mr Simmon.

MR BEAR: So he has got it wrong, has he, in his email?

A. Yes, I think so.

Q. Did you correct that?

A. Again, in the heat of all these events, we were on the phone and it is not necessarily my business to weigh every little word that's been written in an email, and from that perspective, I didn't pay any attention to this specifically.

Q. Is the answer that you didn't correct it?

A. I didn't correct it. I did so by speaking to Vince.

Q. You corrected it by speaking to him?
A. Yes.
Q. When did you speak to him?
A. After these emails, the initial email.
Q. I thought you said in the heat of the moment it wasn't necessary to focus on every little word?
A. No, that's correct, but I did speak about the events, I did speak about a TSC meeting, and explained to them that, listen, this study is really suspended for the time being, this is the message.
Q. By this stage, you'd probably picked up, hadn't you, that Mr Simmon, before 1st November, had become very unhappy with LSHTM, you were aware of that, were you?
A. I think that was already -- if you go back in time a bit, since the beginning of the summer, and to be honest, since I joined as a consultant earlier in 2007, there was a discontent, and I think probably on both sides, and I think I've written that in the statement somewhere, where I say that at a professional level, I do have doubts, but on both sides not only on one side, in the way people communicated with each other.
Again, I do stand for a high level of professionalism, and I thought that that was on a weaker side.
MR JUSTICE BURTON: Just pausing for a moment, when you're

being asked about this sentence, and you say it's wrong, can we backwards on the sentence?

"LSHTM argued for suspension."

Now, there are two or three representatives of LSHTM on the committee.

A. Yes.

MR JUSTICE BURTON: Is that right, that they argued for suspension?

A. I definitely think that's the outcome of that meeting -- of the TSC meeting.

MR JUSTICE BURTON: Yes, but did they argue for a suspension?

A. I think there was a true discussion during that meeting where I put some elements on the table, and where each of the members contributed their own into suspending the trial -- that was one of the conclusions. The other one of course taking the necessary steps of stopping treatment and informing the regulators.

MR BEAR: I'm not sure we can take that a great deal further.

Mr Simmon, I suggest, would have been only too delighted to hear that LSHTM had wanted to stop the trial. That would have been news which he would have regarded as confirming his view of them, wouldn't he?

A. I think that's a very naive statement, and you know why,

because it's in the best interests of a company to complete the product development.

Q. Yes, but Mr Simmon didn't want the company to complete it with LSHTM, did he? You knew that.

A. That is another issue. Yes, I was aware of the disputes, but not at a high level of detail. It's not in my interests. But I think you have to -- if you were a CEO of a company, I think, as you have already been kicking against the shin, if you are concerned about the commercial intent of a company, then this is it, because this is your lifeline, this is what is going to bring the investors on board, to carry this company either into an outlicensing situation or to raise more money. It's not by trying to go into a fight with your CRO, or service provider I should say in this case.

Q. By this stage you were aware that Mr Simmon was hoping to dispense with the services of LSHTM, weren't you?

A. I know that they were having a dispute, but to my knowledge, there was no formal termination of the contract between the London School in regard of this study, and Xytis.

Q. He wanted a termination, didn't he?

A. That has been discussed, yes.

Q. So if you could have given him supervision that would have supported his desire to get rid of LSHTM, he would

have welcomed that, wouldn't he?

A. Okay, if you're in the business of shooting the messenger, it's a very interesting notification, but I think the conclusion of the TSC -- and I think that would have been the nicest way to do it, the chairman of the TSC should have communicated directly with Vince, with the sponsor of the trial.

Q. Let me just be clear why I'm spending any time on this, Dr Goedkoop. In your witness statement, which you confirmed was correct when you started to give evidence this morning --

A. Yes.

Q. -- you said, in terms, that Professor Roberts, who is the chief LSHTM representative, argued for termination of the trial. That's what you said in your statement.

A. That was the first sentence that he started with.

Q. Yes, and do you agree, just as a matter of language, what you said there, in your witness statement, is inconsistent with what we see in the last words of this sentence on page 2803:

"... LSHTM argued for suspension."

A. The last sentence, we're still with this email, right?

Q. Yes, in the middle sentence:

"... LSHTM ..."

A. "One member of the TSC wanted the trial halted, but the

LSHTM argued for suspension."

Q. Yes, and that's not the same thing, is it, as saying that Professor Roberts opened by arguing or stating that the trial should be terminated. They are two different accounts, aren't they?

A. I'm not sure if I follow you. I mean, the outcome was suspension of the trial. This is the --

Q. No, we're talking about what people argued for. Somebody can't argue for suspension and argue for termination at the same time, can they?

A. No, but I --

MR NASH: My Lord, we've been on this for 15 minutes now and he's given his evidence about this document, so --

MR JUSTICE BURTON: Yes.

MR BEAR: Yes, very well, I will move on.

Can I put this to you: you're making up what you say about Professor Roberts recommending termination of the trial.

A. I don't think so. This is what I heard with my own ears.

Q. Let's look at the next but one --

MR JUSTICE BURTON: And did you tell that to Dr Simmon: Professor Roberts started the whole meeting by saying we must terminate the trial, and I persuaded him not to? Did you tell that to Dr Simmon?

A. Yes, I have shared that with Mr Simmon.
MR JUSTICE BURTON: Thank you.
MR BEAR: All right, now:
"We were shocked to learn ..."
Can you see that line?
A. Yes.
Q. "... that there had been 94 SAEs reported."
A. Correct.
Q. That's information that Mr Simmon got from you, isn't it?
A. Correct.
Q. And that information you had obtained from the tables?
A. Yes, correct.
Q. You say in your witness statement that there was an agreement that the data would be treated as confidential?
A. Yes, and it was also an agreement that I could share a qualitative statement and I'm not unblinding a study by giving a total overall figure.
Q. 94 is not a qualitative statement, is it?
A. No, I agree with that.
Q. So you were going beyond what had been agreed, weren't you?
A. Yes.
Q. And what made you feel able to do that?

A. Because I was not jeopardising the unblinding or the potential for unblinding of the study, and I think that is very critical to eventual restart of the study as discussed before.
Q. You didn't go back to Professor Roberts, did you, and say: listen, I want to give out information that is more than merely qualitative; I want to give out some figures? You had no such conversation with him, did you?
A. No.
Q. Do you think you should have done?
A. No, not really.
Q. Was he entitled to assume, in the light of your agreement, that you would not be giving out figures?
A. Yes, I think that's a fair statement.
Q. If we look at, going forward in bundle 10, please --
MR JUSTICE BURTON: Page?
MR BEAR: 2844. Can you look at the top email? This is from Vincent Simmon to Professor Roberts at the end of the main addressee list, and to "Brain Brain", which is the LSHTM general trial email account, and then to various other people with yourself copied in, correct?
A. Yes.
Q. Did you receive this?
A. Yes.

Q. He sends it on 2nd November in the evening:

"Post-suspension questions.

"Dear all, it is very important that Xytis obtain answers to these questions as quickly as possible. I am particularly concerned about the discrepancies in the SAEs. Rene is bound by certain confidentiality issues from disclosing the number of SAEs to us. I cannot understand how informing us of the total SAEs that were discussed with the DSMB should be withheld from us."

You had already told Mr Simmon, hadn't you, what the total number of SAEs was?

A. Yes.

Q. Can you explain why it is that Mr Simmon should be asking LSHTM for that information?

A. I think we -- he wanted to reassure himself that whatever I was communicating was maybe correct, and if you really want to know maybe you should ask Mr Simmon.

Q. You see, he actually says, doesn't he:

"Rene is bound by certain confidentiality issues from disclosing the number of SAEs to us."

But you had already disclosed that number, hadn't you?

A. Yes.

Q. Did you write to anybody and say: hang on a second, I have already disclosed this information?

A. I have communicated that to Vince, and he was aware of that.
Q. When did you communicate that to Vince?
A. In the telephone conversations that we did have.
Q. Did you not think that LSHTM were being misled about what you had and hadn't said?
A. No, I think what we do internally is none of LSHTM's business.
Q. Well, maybe not, but here Mr Simmon has made a statement which implies internally that you haven't given him the information, hasn't he?
A. Well, and then you just cited this other document and you see that it's already there.
Q. Let's look lower down at 2844. This is the email from Mr Furcha on the morning of Friday. So this is sent to Professor Roberts and Ms Shakur:

"Thanks for taking the time to discuss with me yesterday [that's on 1st November]. A few reflections and questions having thought about some of the comments that were made yesterday.

"When I asked you if the HPM database was used for the presentation to the DSMB, your response was 'yes'. However following discussions with HPM, they claim that no listing was provided to the TCC until yesterday afternoon."

And then this sentence:

"Rene has been in the office today and was surprised by the significant difference in the numbers of SAEs reported by HPM and those reported to the DSMB."

That's a different story from the one you've been telling us today, isn't it?

A. No, why?

Q. You told us today that you were immediately struck when you received the tables from the DSMB by the contrast with the HPM information?

A. Yes, and that's correct as well.

Q. Well --

A. Because I --

Q. -- either you knew it at the time, Dr Goedkoop, or you went into the office on the following day, on the 2nd and were then surprised. Which was it?

A. Why is it you are assuming that I did not know about HPM SAE incidents before we had this DSMB, TSC day?

Q. Mr Furcha in this email suggested that this was a discrepancy that had come to your attention on 2nd November when you went into the office. That's what he says, isn't it?

A. Yes, that's his words.

Q. Yes, and you were copied in again, and you didn't seek to correct any of this. It was all a ruse, wasn't it?

A. Well, you know, I'm not in that kind of activity span of, as I said before, weighing every word, and then commenting on it. I'm a proactive person, and if there is an issue that is really critical to the further conduct of a project, then that's another issue. But that was not the case. I mean, I read very quickly through those emails.

Q. You didn't feel it was any of your business to try and correct what was being said by Xytis to my clients?

A. At that time, the London School wasn't your client, I think, and what we communicate internally is Xytis's business, and really not that of the outside community.

Q. You didn't feel it was any of your business to try and correct what was being said by Xytis to LSHTM, did you?

A. No.

Q. Even if you could see -- as I suggest you could -- that they were being given information which was incorrect?

A. So the incorrectness being the time -- the events of time?

Q. Being the implication that you hadn't provided this information.

A. I did provide the 94 --

Q. Yes, and it was said that you hadn't, and you didn't correct it.

A. Okay, well, that's what happened, then.

Q. What other information did you give Mr Simmon about the data that the DSMB had provided you with?
A. Well, that there are the categories, so the overall figure, and that the number of death as reported in that table, as we discussed this morning, was discrepant from the number of patients with SAEs.
Q. Let's -- since you've mentioned that -- no, let's complete it, so the number of deaths. When did you give him that?
A. I don't know exactly. Probably relatively quickly after the first impact of the message.
Q. Right, it wouldn't have been a month later?
A. No, I don't think so.
Q. Would you take up bundle C12? Bundle 12, 3472, please. This is an email from you to Mr Furcha dated 3rd December, which was the day before Xytis made its first application to court, its without notice application:

"Dear Rowland, have been on the phone with Vincent during the weekend and today. I have provided the overall number of SAEs per category pooled data as I have shown to you before, including the number of patients with an SAE, N equals 38."

N means number, doesn't it?
A. Yes, correct.

Q. "Interestingly, the number of death N equals 42 is already higher than the number of patients with an SAE. Something is strange, because it allows patients to die twice or the database is just crap."

This was a point you thought of on 3rd December, wasn't it?

A. Yes. If I see inconsistency in data, then I do question either the database or the information that went into it, or the way it was analysed.

Q. I just want to be clear that you understood my question, because I know English isn't your first language. This is a point that you'd thought of on 3rd December, do you agree?

A. It's what I already thought of when I saw the DSMB table for the first time.

Q. It doesn't read that way, does it? Do you agree?

A. No, it doesn't.

Q. How do you explain the way you wrote it?

A. It's my style of writing. I've provided the overall number of SAEs per category, blah blah blah blah, including ... So I have done that. So that's already before this message.

MR JUSTICE BURTON: When did you make the notes on that document that we've been looking at?

A. This was written on --

MR JUSTICE BURTON: No, the document we looked at this morning.
A. That was on 1st November, just before we had --
MR JUSTICE BURTON: So you made those notes, which included your noticing the difference between 38 and 42 at the time?
A. Annotations, correct.
MR JUSTICE BURTON: But you didn't pass that on to Dr Simmon until 3rd December, is that it?
A. Well, I think we kind of discussed it before I sent out this message, yes.
MR JUSTICE BURTON: You did give this information to Dr Simmon at some stage between 1st November and 3rd December, did you?
A. Yes.
MR JUSTICE BURTON: It's being suggested to you that it looks like it's the first time that you're mentioning, at any rate to Mr Furcha, this point?
A. That's correct.
MR JUSTICE BURTON: What's correct?
A. No, I've been open with Dr Simmon and we have tried to do everything to keep Rowland out of that picture -- Mr Furcha.
MR JUSTICE BURTON: I see, so you discussed it with Mr Simmon before --

A. Yes.
MR JUSTICE BURTON: -- but you hadn't raised it with Mr Furcha, is this what you're saying?
A. Yes.
MR JUSTICE BURTON: And you hadn't done that because Mr Furcha is someone who you shouldn't have been disclosing it to?
A. Well, he's more involved in the day-to-day issues, and I think in my report, my line was Vince and not with Rowland in that regard.
MR JUSTICE BURTON: But you shouldn't have been disclosing it to him, because this is unblinded information?
A. No, I think at the same time -- this is blinded data.
MR JUSTICE BURTON: This isn't blinded data.
A. Excuse me?
MR JUSTICE BURTON: The 38 and 42 inconsistency is unblinded data.
A. It is blinded data because it's only referring to the totals, as we discussed this morning, and not to individual dose groups or treatment arms. And the reason why Rowland and I were discussing these kind of things, it's because we tried to understand what was really playing in the background, independent of whatever the outcome may be.
MR BEAR: If we go to look at core bundle 2, tab 18, please,

to look at the tables again. At tab 18, looking at the DSMB tables, if we go to page 2761, the table at the top, and we look at the "yes" line -- are you with me so far?

A. Yes.

Q. -- we can see the total number of patients at the end of the row is 38?

A. Correct.

Q. So that is the total number of patients with an SAE or more than one SAE. Where do we find the number of deaths, please?

A. I think you should go to page 2763 in the middle where the SAEs are categorised, and there is one line that reads "deaths", and if you look at the last column, it says "42".

Q. That, I suggest, is not the number of deaths but it's the number of serious adverse events by category, looking at the top, and:

"Note: each patient can have more than one event in each category."

A. Yes, except for that death is an outcome, and you can only die once.

Q. But you can have more than one serious adverse event leading to death, can't you?

A. Sure, yes, but the outcome, as I said before, is death,

and so you don't count that number of events, you count death.

Q. That's not what this heading is saying, is it? When it says:

"each patient can have more than one event in each category", that means that you can have more than one event per patient in the death category. That's what it means, isn't it?

A. If you -- okay, I follow the protocol, and if you go with the definition of each of these categories, then I think it's clear that death is an outcome, and I think you can only have one outcome in this particular case, and that's death. It's pretty --

Q. I wasn't asking you about the protocol; I was asking you about the meaning of the heading, okay?

A. Yes, I think I agree with what you're saying.

Q. Yes, and the DSMB's tables are not specified in the protocol, are they?

A. No.

Q. No, because they're an --

A. That was in the chart, I think.

Q. -- interim analysis. Yes. So in fact an informed medical person familiar with clinical trials looking at this table would understand, wouldn't he, that the total number of 42 could be greater than the total number of

individual patients who had died?
A. No.
Q. He wouldn't understand that?
A. No, not when it comes down to --
MR JUSTICE BURTON: Can you put it more simply to the doctor and to me?
MR BEAR: Yes. You agree with me, I think, that each patient can have more than one event in each category, including death?
A. No, you will have to go back to the protocol and read the definition of each of those categories --
MR JUSTICE BURTON: Well, let's leave the protocol for the moment.
A. Okay.
MR JUSTICE BURTON: I'm just trying to understand the table. This table is:
"Number of serious adverse events by category."
Then there's the note which we come back to.
A. Correct.
MR JUSTICE BURTON: Then we have an apparent description of the serious adverse events, one of which is death, one of which is life threatening, hospitalisation, disability, medically significant. I can entirely understand -- and I think you're saying you understand -- that a patient can have more than one

serious adverse event --

A. Absolutely.

MR JUSTICE BURTON: -- because he can begin by medically significant, he can become disabled, he can get hospitalised, he can have his life threatened and he can die. So somebody could have five of these.

I'm trying to understand what the death category means in here, and I think you're saying that your understanding is that you can only die once, and, therefore, even if somebody has more than one serious adverse event, he only gets one death, and that this is intended --

A. Correct.

MR JUSTICE BURTON: -- to categorise the number of deaths in the serious adverse events category.

A. That's correct.

MR JUSTICE BURTON: And that's what this is doing, breaking it down, and therefore you regard this as saying that 42 patients died, which is inconsistent with 38 patients dying?

A. Correct.

MR JUSTICE BURTON: You and I are together. Now, both of our understandings have got to be punctured by Mr Bear.

MR BEAR: Yes. The categories are: death, life threatening, hospitalisation and so on, aren't they, correct?

A. Yes.
Q. So a patient in the category of hospitalisation, for example, can have more than one serious event in that category alone, can't he?
A. No, the serious adverse event is hospitalisation. You can only be hospitalised once.
MR JUSTICE BURTON: He can go back into hospital a second time.
A. Yes, but then it's a second hospitalisation, and then it's a second adverse event, serious adverse event.
MR BEAR: Let's break it down, and this may take a little time, because it's important. Let's look at the heading first of all:
"The number of serious adverse events."
Okay? Can you look at those words?
A. Yes.
Q. So when we talk about the number of events, that's not the same as the number of patients, is it?
A. No.
Q. Let's look at "life threatening", okay? Somebody can have more than one life threatening event, can't they?
A. Yes.
Q. So in that case, there will be more than one entry for that patient for that category. Do you agree?
A. Yes, for death category.

Q. No, I wasn't talking about death; I was talking about life threatening.
A. And I was talking about the same, yes.
Q. Now, when we talk about a serious category or as serious as a category of death, what we mean is we mean an event which causes or contributes to death, correct?
A. Again, if you go back to the definition of death and the serious adverse event -- and I will not cite protocol --
MR JUSTICE BURTON: Do try the protocol, if you want, because we've all got to understand.
A. This is an outcome measure, and it has to be reported independent on whatever the underlying cause is for the death, and it could be a combination of various elements. But you cannot have more dead patients than the number of patients you will --
MR JUSTICE BURTON: This is where you seem to be differing. I do want to try to understand.
A. Yes.
MR JUSTICE BURTON: You're saying something that I as a lay man can understand: you only die -- apart from James Bond, you only die once.
Now, what's being suggested to you by Mr Bear, is that you can actually have a serious adverse event called death more than once. I think that's what Mr Bear is saying. Now, that's what we've got to get

to. A patient can have a death, in the sense of death defined as an SAE, more than once.

Now, have I got that, Mr Bear, and obviously you'll have to explain how that can be, but I think I've understood your case?

MR BEAR: Yes, what I'm going to do is I'm going to put a bit of Professor Roberts' statement to Dr Goedkoop.

MR JUSTICE BURTON: Yes.

MR BEAR: If we look at the witness statement bundle, and within that at tab 5, you should have something which is headed:

"The third witness statement of Professor Roberts."

Have you got that?

A. Yes.

Q. Could you turn to page 35, please? I want you to look at the foot of the page at 125. Do you see 125:

"Mr Simmon complained [this is in a witness statement that he made earlier] that the DSMB data showed 42 deaths but only 38 patients with an SAE. They do not. They show 42 SAEs linked with deaths.

A patient may well have more than one SAE, for example cerebral oedema and pneumonia. These are logged as two SAEs. If the patient dies, both SAEs will be recorded as linked to a death."

That's correct, isn't it?

A. Yes, so -- and what you will do in your report is only have one death, you write a narrative, and you describe all the events that led to death.

Q. That's in the safety report?

A. That would be in a safety report, it would also be in a scientific publication. You cannot report more death patients than the number of patients that you have.

Q. Yes, but the point that we're on is that you can report more events than deaths, because more than one event can contribute to death.

A. That is something else. Here you're talking -- you're -- you have to go back to day one, and this is how the data -- how this table was presented to me, and from what I've been reading, I could not make that link that there were more than one events leading to death and hence every event that led to death would actually be counted as a separate death.

I mean, personally, I don't see the logic of it, but I leave that in the middle.

MR JUSTICE BURTON: Is there anything by way of either this protocol or this trial, or learning generally, which indicates that you must report under the category "death" a cerebral oedema which leads to death as well as a pneumonia which leads to death so that you can have more than one death report for one patient?

MR BEAR: Yes, the case report form categorises --

MR JUSTICE BURTON: Can you show us that?

MR BEAR: Yes, it's in core bundle 1.

MR JUSTICE BURTON: This looks as though, Dr Goedkoop, this isn't something that you knew about. Whether it's something you should have known about is something we'll no doubt hear.

Now where are we? In core bundle --

MR BEAR: Tab 4 of 1.

A. If I may say something --

MR JUSTICE BURTON: Hold on, just let's understand it first and then say what you want to say. Don't forget what you're going to say.

Tab?

MR BEAR: Tab 4.

MR JUSTICE BURTON: Core bundle 1?

MR BEAR: Yes, this is the adverse event form.

MR JUSTICE BURTON: Have you got core bundle 1?

A. Which tab, please?

MR BEAR: Tab 4, thank you.

A. Yes.

Q. If you look at the second page, you'll see -- are you familiar with this at all or not?

A. Yes, yes.

Q. So column A is headed "adverse event". So each medical

event that is adverse has to be separately recorded there.

A. Absolutely.

Q. And then if we go across to column G, each event has to have a rating in column G, doesn't it?

A. Has to have what?

Q. A rating, a code or category in column G, an entry.

A. Yes.

Q. And then we can see what they are in the middle of the heading.

A. Mm-hmm.

Q. So somebody could have a stroke and a heart attack and both of those could contribute to his unfortunate death, is that right?

A. What you are looking at is how you collect data, and what we are seeing in the DSMB table is how you report it. Those are two different elements.

Q. Well, shouldn't they match one another?

A. Ultimately, yes, it depends on how you analyse, but --

Q. Wouldn't it be reasonable to assume, unless you have some very good evidence otherwise and have found out that it's not the case, wouldn't it be reasonable to assume that they do match the collection and the reporting?

A. Absolutely, but this is why, when you report serious

adverse events, a narrative is written, and this is where the expertise of Professor Roberts or the clinicians come into place, and they write with a common narrative: patient had symptom A, B, C and D, that led to death in this particular patient. You say something about the patient history, including treatment, et cetera. This is how it gets reported. This is how it gets communicated to authorities.

Q. But on the trial -- yes, that's the pharmacovigilance aspect, I understand that.

A. Yes.

Q. But on the --

A. But it will also be the same in a scientific summary leading to a publication.

Q. Well, that's not correct, is it?

A. -- a report.

Q. Because this trial is designed to collect data by reference to categories, so that each adverse event has its own category of seriousness. Do you agree that that's how this trial is designed, first of all?

A. Well, it's an obligation to do it by category.

Q. No, by the categories that we see here.

A. Yes.

Q. So the way the DSMB was looking at the data was not to go into the detail of what precisely might have been the

particular medical reasons for the particular patient, but to look at a comparative pattern, if there was one, of events of a particular type of seriousness between the different treatment arms. I've got that right, haven't I?

A. Yes, I'm not contesting what the DSMB has done.

MR JUSTICE BURTON: I thought you were saying: look at this table, 38, look at this table, 42. That is such a nonsense that it shows something has gone wrong somewhere.

Now it's being suggested to you that because of the way in which this trial had to be reported by reference to the CRF forms, it was not only not an indicator that anything had gone wrong, but it was the only proper way to report it and it showed no inconsistency at all, and that you should have known that. That's what is being put to you.

A. Okay, may I say something?

MR JUSTICE BURTON: Yes.

A. Okay, the way I receive the data, I interpreted it as I saw fit on the basis of the information that is on that sheet, and personally I could not have figured out that they were reporting death and, if there were two deaths in one patient that that would be an appropriate way of reporting.

But I will leave that in the middle.

The notion that you can have more death than the number of patients is very odd to me, and it will never be reported as such. If you want to talk about the number of clinical adverse events, that's fine, but this is an outcome measure, this is not an event in itself.

MR BEAR: Do we at least agree on this: do you accept, having heard what I've said -- or perhaps having looked into it in the course of preparing for the trial -- that the database doesn't record the number of deaths as 42; it records the number of events leading to death as 42? Do you agree with that?

A. That's what you're telling me now, yes.

Q. Do you agree?

MR JUSTICE BURTON: Shouldn't you have known that at the time? If you look at the form which is still open in front of you --

A. No --

MR JUSTICE BURTON: Hold on. The outcome is a separate column. D, look at D, outcome, "died" is number 5 on an outcome. So it does appear to be -- at any rate what's being suggested to you is that one would have the adverse event, which would be calculated according to its seriousness, and there could be two or three of them if the patient had three simultaneous adverse events all

of which within a very short time led to death, so his outcome would only be one death, but there could be three adverse events which would qualify under "death" as opposed to "life threatening", because life threatening fortunately wouldn't be likely to be the outcome -- or at any rate wouldn't have been the outcome of death.

Now, all that's been asked is: was it really appropriate for you to have regarded that as something odd to see recorded in this data as a member of the TSC?

A. I do think so, yes, I do think it's strange, and I may be very repetitive, but I don't understand how you can report more than one death in one patient, and I know that there is a way of collecting data, but there is another way of reporting data.

MR BEAR: Could you look at page 2771, please, in tab 18? Look at the bottom of the page about three or four centimetres up. Can you see the heading:

"All cause mortality to day 15"?

A. Correct.

Q. Okay, and then if you look at the top left-hand bit of the table:

"Died up to day 15."

Do you see that?

A. Yes.

Q. This is going to tell us how many deaths there are, isn't it?
A. Yes.
Q. If we look at the "yes" row and travel along to the right, the total is 26, isn't it?
A. Yes.
Q. So actually in the tables, Dr Goedkoop, it tells you that the number of deaths is less -- 26 -- than the number of patients with an SAE -- 38?
A. Yes.
Q. It's there on the face of the document, isn't it?
A. Yes. That brings me really to the discrepancy again to the HPM database --
Q. The point I'm making is that your argument, that you had no way of knowing that the number of deaths was not 42, is incorrect, because we can see here in the table the number of deaths is 26.
A. Yes.
Q. So your argument is wrong, isn't it?
A. I think so, if you are focusing on this one, but the way it was reported -- and you go back a few tables -- then I come back to the same argument.

The point is, I don't know which data was correct.

Q. So you're prepared to assume, are you, that this trial -- which is run by a well-known trialist,

Professor Roberts, do you agree with that, he is well known?

A. I didn't know him before, but ...

Q. Do you agree now that he is well known?

A. In a certain community, but I'm not discussing reputation here.

Q. Do you agree that the members of the DSMB are well known and very experienced?

A. Within the academic environment, yes.

Q. All right, within whatever environment. Your assumption would have meant that they had all made a ridiculous mistake, wouldn't it?

A. No. I think I'm entitled to have an opinion on the way data is presented to me, and to interpret it. This is also why you come together as a TSC, and you discuss whatever needs to be discussed.

Q. Did you discuss the number of deaths with the TSC?

A. No.

Q. It's a point that you have dreamt up later or that someone else has given to you, isn't it?

A. No, because if you go back to my notes you already see that I made an annotation on my own document.

Q. Let me briefly ask you some questions about paragraph 10 of your --

MR JUSTICE BURTON: If you're leaving that, can I ask you to

look again at 3472 in the chronological bundle. It should be open still. I'm afraid I don't know what chronological bundle it is because I've taken it out and put it in the core bundle.

MR BEAR: C10.

MR JUSTICE BURTON: Thank you. 3472.

A. Yes.

MR JUSTICE BURTON: Having heard what you've heard now, the explanation, seen the format of the CRF form or the report forms which are drawn from the CRF, and the distinction between adverse event and outcome, do you still stand by your criticism which you make in page 3472 when you say:

"Something is strange because it allows patients to die twice or the database is just crap."

A. I stand by the notion that I don't understand how patients can die more than once.

MR JUSTICE BURTON: Because patients can't die twice, this database is "crap", is that right?

A. No, the "crap" I think refers to many other discussions that we had where --

MR JUSTICE BURTON: No, I'm asking you whether you stand by your opinion, which you gave in this report, to Mr Furcha, 3rd December, that by virtue of the fact that people -- "that either the database is allowing patients

to die twice" -- which obviously is a physical impossibility -- "or it is just crap", that was an opinion you've expressed. Do you still stand by that opinion?

A. Yes.

MR JUSTICE BURTON: Thank you.

MR BEAR: Very briefly, if we could go to Dr Goedkoop's witness statement in witness statement bundle 1 -- you might want to do a little bit of housekeeping to prevent a collapse of bundles -- witness statement bundle 1, my Lord, at paragraph 10 on page 3 of the statement.

I want you to look at the line which begins, eight lines up from the bottom of the page with the word:

"Thirdly ..."

I wanted to look at the sentence beginning, towards the end, beginning with the word:

"Finally ..."

A. What item are you at?

Q. Sorry, page 3, paragraph 10. If you count up eight lines from the bottom of the page and then towards the end of the line you have a sentence beginning:

"Finally ..."

I'm very happy for the young lady from Dechert to point it out. We're on the witness statement on page 3, eight lines from the bottom.

MR JUSTICE BURTON: "Finally, and perhaps most importantly ..."

It's the line that begins:

"Thirdly, there was resistance ..."

A. "Thirdly there was resistance ..."

Okay.

MR BEAR: Towards the end of that line:

"Finally, and perhaps most importantly a major concern was a clear disconnect between the HPM and the LSHTM SAE figures. I recall discussing this issue with Rowland during August and assisting Vince Simmon with the drafting of a letter to Professor Roberts setting out various concerns about the performance of LSHTM. One of the concerns raised [then that should be "was"] the discrepancies between the SAE information held by HPM, who had responsibility for pharmacovigilance, and that held by LSHTM, copy letter of 18th August 2007."

Can we then take up that letter which your Lordship may have put in the core bundle, but I'm going to take from chronological bundle 7, please, at page 2014.

Is this the letter you're referring to?

A. I think so, yes.

Q. The subject is BRAIN Trial communication plan, and then if we just glance down the page he wants a progress report every two weeks to contain the following

information: patient recruitment, screened patients, initiated sites, over the page, ethics committee status of new sites, status of protocol amendments, and then SAEs:

"It seems that there are some discrepancies between HPM and TCC databases. This needs to be rectified."

Is that what you're referring to?

A. Mm-hmm.

Q. The concern that's being expressed here isn't a scientific concern; it's a concern about communication, isn't it?

A. Yes, definitely that (inaudible).

Q. Then if we turn forward to look at the further correspondence, if you go in the bundle to 2080 --

A. There is a communication concern, but there is also a concern that may relate to the reporting duties that one has for the serious adverse events in relation to the regulators.

Q. I see, so pharmacovigilance?

A. Correct.

Q. Okay, and then if we look at 2080, please, further on in the bundle, this is where we have to be slightly careful because the original was coloured and we don't -- technology hasn't given us that luxury. We're still in black and white, I'm afraid, in courts here. Look at

2081. Can you see -- perhaps I should just tell you, so this is dated 30th August, starting on 2080, and what's happened is that Professor Roberts replied by putting his comments into the letter -- although the font seems to have changed -- and then, in orange, although not for us, Mr Simmon is putting his comments back.

So if you go over to 2081, if you could look on the third last chunk of text on the page, or the fourth last, sorry, there's a round bullet point:

"SAEs/deaths."

Do you see that?

A. Yes.

Q. Then Professor Roberts has said:

"There has to be some understanding from your team that there will always be discrepancies between the two databases ... resolutions are constantly ongoing and will only be finally resolved at the end of the trial when there is a planned comparison of the two databases reporting to Xytis."

Did you see that?

A. This?

Q. Yes.

A. Yes.

Q. Was there anything wrong with what Professor Roberts said there?

A. No, I don't think so.
Q. And then looking at what Mr Simmon said in response, beginning:
"Yes, we agree ..."
MR JUSTICE BURTON: Just underneath.
A. Yes.
MR BEAR: If you could just cast your eye over that.
MR JUSTICE BURTON: It's the next paragraph:
"Yes, we agreed ..."
Do you see that?
MR BEAR: "Yes, we agreed agree and understand that at any moment in time discrepancies can exist between the TCC database and the HPM databases. However, we would like to know that such discrepancies are being resolved in current time. We do not want the discrepancies to accumulate until the end of the study, at which time resolving them could add months to the conclusion of the study. Therefore the status of the discrepancies should be reported monthly so that we can ensure that SAE discrepancies have been dealt with in a timely manner."
Pausing there, I suggest the only thing that Mr Simmon was interested in, which is understandable enough, was not having a backlog of work at the end of the study, which would then delay final publication.
A. It is that element, and there is the element of

completing the reporting as you should do in pharmacovigilance, as you just said yourself.

Q. Do you agree with me that he only mentions the first of those two elements in this comment?

A. Yes.

MR BEAR: Thank you very much. We can put that bundle away now.

Thank you, I don't have any further questions.

Re-examination by MR NASH

MR NASH: Dr Goedkoop --

A. Can I come down?

MR JUSTICE BURTON: Hold on, you may be asked some further questions.

MR NASH: You are not quite yet finished, Dr Goedkoop. One or two questions arising from your answers. Bear with me one moment. I'll go back to what you said this morning.

You were asked some questions about the efficacy figures that appear in those tables from the shell table. The reference for those who've got it is at page 67 of the rolling transcript at line 24.

It was put to you that what one could tell from those efficacy measures is that Anatibant increases the degree of neurological impairment. Your response to that was:

"I don't know because the data as presented is reflecting numerical changes but not a change from baseline in these patients, so I just cannot draw that conclusion."

Could you explain the significance of the baseline point?

A. Okay. I think when somebody drops off his bicycle, in example, there are different ways of doing so. You may have a different level of traumatic brain injury. After all they're identifying patients with moderate TBI.

So the baseline value that you give, either to the Glasgow Coma Scale or the Hireos scale, may be different between patients in a group, in a dose group, treatment arm.

Now, in order to normalise for these figures, for these variations, at baseline, there is a way of doing that, and that's by looking at the change from day one -- so the baseline -- until the day that you want to do your measurement -- in this case day 15.

That difference you can calculate into an -- how you call it -- a percentage, and then you can calculate the mean within a treatment arm, and that's a quite common approach in trying to understand in highly variable population at baseline if there are true differences, yes/no.

Q. So if we can just put that into the focus of the tables we were looking at, if you take up core bundle 2 again, please, and go behind tab 18, and go to page 2765, we'll take the first one, which is the Glasgow Coma score at day 3 on this page.

A. Correct.

Q. You have a series of readings for each of the dose groups and the placebo group. What you've just described to us, is it possible to find that difference between baseline and final result from the table which we see on page 2765?

A. No, not from this table, bought the baseline scores have not been mentioned as such in the table. What I'm trying to get to is, there may be an adverse -- what was the wording again, you said it before, like there was in the DSMB report.

Q. Neurological impairment? Or, the DSMB?

A. Adverse event towards the efficacy, right?

Q. Primary analysis?

A. Yes, but the true question here is whether the drug is detrimental to the Glasgow Coma Scale or that neurological surrogate end point, or that there is less improvement from baseline. And those are two different things, in my mind.

So it could still be that the drug has some kind of

activity, I don't know. I mean, I'm just thinking out loud here, and that's what I did when I first saw that data as well.

Here you're only looking at a specific time point. You take a snapshot and you compare A to B, that's basically what you're doing.

Q. The question that was put to you was that the drug tends to increase the degree of neurological impairment which I think is, to my reading, means that the drug is actually causing you harm. Do you agree that that is a conclusion one could draw from this material?

A. I cannot draw that from this table. I can only draw from this table that at a specific time point you take a snapshot and you compare A to B, and you see that there is an end difference.

Q. I understand that.

You can put that bundle away now for a moment. I'm sorry, could you pull out core bundle 2 again, in fact, and go to tab 45?

This is the letter from Professor Sandercock to Professor Roberts on 1st November. Two questions arising from this.

Firstly, your attention was directed to items (a) and (b) on this letter.

A. Correct.

Q. It was suggested to you that these items -- each of these items independently would justify the decision that was taken to suspend the trial. In other words, leaving aside item (a), item (b) was also a pointer in that direction.

Is that a proposition you agree with?

A. Yes.

Q. So each of them independently would have that result?

A. Yes.

Q. Then it was also suggested to you that you never indicated that you had a disagreement with the DSMB's decision. Would you please read the middle paragraph of that letter again, please?

A. "The committee was unanimous in recommending that the steering committee be made aware of the unblinded data with a view to closing recruitment on the grounds that~..."

Q. Et cetera. What was your proposal to the TSC?

A. Well, again, I reflect to the opening words of the chairman, and it was kind of put forward to terminate the clinical trial, and I urged -- I requested to have a discussion on this in terms of changing that to suspension until further notice, and I have no issue with the TSC coming to a conclusion to stop further treatment of patients. I think that is out of the

question, basically.

MR NASH: Thank you, Dr Goedkoop. I've no further questions. Does your Lordship have any questions?

MR JUSTICE BURTON: No, thank you very much, Dr Goedkoop. You're released. You don't need to come back again. You're finished now. You were only available today, weren't you?

A. Yes, I have to go somewhere else.

MR JUSTICE BURTON: Thank you very much for staying.

A. Thank you very much.

MR JUSTICE BURTON: Should we have the short break now before the next witness. Is that a sensible course?

How are we doing on an agreement of the confidentiality arrangements?

MR NASH: We haven't spoken, I think that's for after court, my Lord.

(3.10 pm)

(A short break)

(3.15 pm)

MR NASH: My Lord, Dr Simmon.

My Lord, Dr Simmon has made some notes on one of Professor Sandercock's schedules which he'd like to have with him in the box, if he may. I've spoken to my learned friend. He says he doesn't mind so long as he can look at them.

MR JUSTICE BURTON: Any objection, Mr Bear?
MR BEAR: No, I may want to look at them, but other than that of course not.
MR JUSTICE BURTON: Thank you.

DR VINCENT SIMMON (sworn)

Examination-in-chief by MR NASH

MR NASH: Do remember to keep your voice up, Dr Simmon.
MR JUSTICE BURTON: Yes, it's got to be very clear so we can all hear it. That does not amplify your voice, though speakers; they simply record them. So don't rely on the microphones to amplify.
MR NASH: Dr Simmon, can you give the court your full name, please?
A. Vincent Fowler Simmon.
Q. And your address, please?
A. 6 Lantana, Newport Coast, California, USA.
Q. Can you take up firstly the first of the witness bundles marked 1, witness statement 1, and then look behind tab 1 within that bundle, and you should find there your sixth witness statement. Will you just confirm that that is your statement for the purposes of these proceedings?
A. Yes, it is.
Q. And is everything you say in there to the best of your knowledge correct?

A. I'm looking just to see the date, because I have new information, so as of the date I wrote this, everything in here was correct to the best of my knowledge at that time.

Q. We'll come on to the other matters in a moment, but before we do that, can you look also behind tab 8A within this bundle? And again look at that and confirm that that is also a witness statement made by you for these proceedings?

A. Yes, it is.

Q. And, again, is everything in there to the best of your knowledge correct?

A. Yes, it is.

Q. Can you now take up, please, the second witness statement bundle?

MR JUSTICE BURTON: The same question of you, Mr Nash. I've pulled out the famous paragraph 99 of the first witness statement, but I haven't read anything else. If it's just for the sake of formality that you're going to put these in, then I suggest you can do it conglomerately, but if you are wanting them to be substantively in evidence in the trial, I ought to be -- I ought to read them, or at any rate be asked to read them.

MR NASH: We're going to go to paragraph 99 in a moment, my Lord, but I'll do the conglomerate formality first.

If you look behind tabs 9 through to 13 of this bundle, please, Dr Simmon, and confirm that those are a series of statements 1 to 5 that you've made in these proceedings?

A. Yes, these are the documents which I prepared and signed which were accurate to the best of my knowledge at the dates that they were prepared and signed.

Q. Before we look at some of the detail of those statements, Dr Simmon, can you please explain shortly your experience in the management and conduct of clinical trials?

A. Yes, sir.

First, I'm a PhD, not an MD, in molecular biology from Brown University. I first became responsible for running clinical trials in 1990 as the CEO of Alpha One Biomedicals in Washington DC.

In that capacity, I ran four or five clinical trials with two different drugs, one Thymosin Alpha-1, and one a potential AIDS vaccine. During that I worked with investigators such as Peter Volberding at Stanford, one of the world's most renowned experts in AIDS. I worked with Tom Merrigan at Stanford, another one of the world renowned experts in AIDS who was looking at Interferon as a treatment, and I combined my drug with his Interleukin that he was looking at.

So these were principal investigator initiated studies.

I also ran a study in Hepatitis B, or had a study run under me I should say properly, in Hepatitis C, combination therapy with Interferon.

Both of these studies were initially initiated with a Professor from very -- well, one was with an MD at an Air Force base, in Hepatitis C, and one was with a professor at Wayne State University in Hepatitis B.

Q. Sorry, cutting across you there, Dr Simmon, your role in these various studies, can you just --

A. I was a CEO of Alpha One Biomedicals at the time, so I had a signature responsibility as the sponsor of these trials. Meaning, ultimately, if there was a problem it filters up to the sponsor of the trial as defined, the person who is providing a drug and financial support for the trial is the sponsor. He may delegate certain responsibilities, as we have in this trial, to the London School. But I was CEO at that time, yes.

Q. And what is your degree of knowledge of the regulatory environment, the FDA and the ICH-GCP?

A. I was -- I always had consultants to me on those issues who were quite familiar with the regulations, which since 1990 have changed considerably over time, and require that people who are involved in clinical trials

to register ethical drugs, new pharmaceutical products which all of these were -- I was not dealing with any approved drugs except in combination -- so all of the drugs that I was working with were new pharmaceutical products that had never been shown to be safe or effective in man.

So what it required is, because the guidelines over time changed, that you have expertise that you obtain from various sources, and I usually hired somebody, either as a full-time employee, an MD working for me, or as a consultant who then provided that expertise to me, which I did not personally have.

Subsequent to those trials, I was at Cortex Pharmaceuticals, and I ran trials with Tom Chase at the National Institutes of Health in Alzheimer's Disease, ran a clinical trial with Danny Weinberger at the National Institute of Medical Health in Schizophrenia, with Don Goff at Harvard in Schizophrenia.

Q. I think it follows from all of that that you would describe yourself as very experienced in the management of clinical trials for new medicines?

A. Quite experienced, sir, and there were several other ones I've run I would mention. As COO, when I was at Merrimack Pharmaceuticals, I ran two clinical trials, one in rheumatoid arthritis, it was about 240 patients,

and one in psoriasis, which was about 20 patients.

All of those trials, with the exception of the AIDS vaccine, which did I with Peter Volberding and his publishers, in abstract, were phase 2 trials, and the goal of all those trials was to see if we could get a signal of efficacy in a relatively small patient population.

I was also CEO of Cortex when we ran in conjunction with Servier, a French company, an international trial which enrolled over 400 patients in mild cognitive impairment.

So I have a great deal of experience as a CEO in the requirements and the standards as they changed in running clinical trials which are to register new drugs that have never been shown to be safe or effective in man previously.

Q. Can we take up, please, your witness statement in witness statement bundle 2.

First witness statement made in these proceedings, behind tab 9, and within that statement, please go to paragraph 99 which is on page 24.

A. Yes.

Q. And that paragraph contains a table, and you explain what is in that table and make some comments on it between paragraphs 99 and 101. Do you want to just

remind yourself for a moment now what you say there? (Pause).

A. Including 101, did you say, sir?

Q. Yes, including 101, yes, please. Then go forward, please, to tab 11 within the same bundle to your third witness statement, where you make some further comments on the table between paragraphs 5 through to paragraph 11. And again I'd ask you to remind yourself what you said there. (Pause).

A. Reading it quickly, I've refreshed my memory.

Q. The point you're making in those two statements, Dr Simmon, is that there appeared to be a significant difference between the HPM database and the SAE record held at the school, and that the SAE record held at the school was the basis of the submission to the DSMB. That's right, isn't it?

A. That is correct. That is my belief.

Q. Having had the opportunity to look at other documents which have been produced in the course of this litigation, do you still maintain that there is a significant difference between the two, and if you do, can you explain what you view as being the significant difference?

A. First, I did receive from Dr Goedkoop the information around the weekend of December --

preceding December 5th.

The information you see in the last column here, which is -- I would characterise this as blinded as did Dr Goedkoop for the simple reason we get similar kinds of information, my Lord, from HPM. We get this kind of data from HPM already. It's not categorised by which group of patients had these events; it's only their totals. So I can't tell anything from this other than gross numbers. It's blinded, by anybody's standard.

The -- secondly, I have listened carefully, and I understand better today, as a result of the testimony from Dr Goedkoop that Mr Bear elicited, how they use a term that was confusing at the time, so that what I thought was number of deaths -- and I received this verbally without getting any tables or anything like that. So I got a phone call from -- or I initiated -- whatever -- a phone discussion with Dr Goedkoop regarding these numbers, and so I now understand the distinction and would withdraw today an argument although I think it's confusing here, it may be because the shortcut of the words "deaths" is used here versus the rather more elaborate description that exists in the tables that Dr Goedkoop referred to.

Q. Pausing there, we're obviously talking there about the apparent discrepancy between 42 adverse events leading

to deaths and the number of patients who died. That's not a point you maintain now?

A. I would withdraw that now, based on the discussion that preceded my current testimony, yes.

Q. I understand.

A. I think it would be a waste of our time to try to bury in on that point any longer. It's been adequately discussed and explained.

Q. What's your position about the discrepancy between the HPM database and the TCC SAEs as of today?

A. Again, there is an issue here which is now in my current knowledge that wasn't at the time I prepared this table, because I was not privy to completely where this information came from, but this TCC extract, which I originally thought was equivalent to the DSMB extract, it turns out is really the HPM -- what we believe is the HPM data or equivalent to the HPM data that exists in the data dump, okay?

So that data should be -- and in fact is -- quite comparable with the data from HPM. They should be closely aligned and reasonably, I say, they are. Given that there are certain time discrepancies between events getting put into computer databases.

There are six events I haven't recorded which were in part of that -- my witness statement too. There

would be allocated among number of deaths, number of prolonged hospitalisations, life threatening SAEs -- the reason I didn't allocate those as can be apparent from witness statement 2, page 3, is that there are multiple descriptions of those events, or at least two descriptions, one, death or medically important, life threatening or hospitalisations. I didn't know where to allocate those, so to avoid me making the decision, I just left them out but tried to explain why I had done so.

Q. I think you're probably losing us on that level of detail, Dr Simmon.

A. Sorry.

Q. What I am interested to know is where you stand on the main points which you're making here.

A. Okay. So the biggest concerns I have is, the number of SAEs total and the HPM database, 49, or the TCC extract which was from the London School, 56, and the DSMB number, 94 -- So 94 is almost twice those other numbers in terms of magnitude.

MR JUSTICE BURTON: Is that the only complaint that you now stand by, out of this table?

A. No, sir. Also the number of other medically relevant SAEs is 37 in the DSMB extract versus 4 or 1 in the other two. So those are the two concerns that I have

with the information that was provided to the DSMB, represented by this summary of that information.

MR NASH: Thank you. I think you can put that document away for the moment.

We're now going to look at some blinded information, so, again, those who can't see it will need to leave -- I meant unblinded information of course.

Will you take up witness statement bundle number 1, and go to tab 6, Professor Sandercock's statement.

If you go behind his statement, you'll see that he has appended three tables, 2A, 2B and 2C?

A. I see that.

Q. Have you had the opportunity of studying those tables?

A. Yes, it's just this particular version has got two copies of table C in it, but that's -- I have.

I received these tables yesterday.

Q. What conclusions have you drawn from looking at those?

A. I apologise, my Lord, I don't know the process here, but I have notes on this, and Mr Bear, I believe you wanted to see them?

MR JUSTICE BURTON: As long as the other side can see them in due course you can use them in the witness-box to refresh your memory. You made them yesterday, I assume, when you read the documents?

A. Last night, yes, sir.

MR JUSTICE BURTON: Yes.

A. Okay, I only have a few comments, but I think they're quite relevant.

What I did on table 2A is I used a notation "N", for number, and then I counted up in the treatment group -- I'm looking at table 2A, first line "yes" and I have a number 38, which is a number we've talked about before from the tables, and Dr Goedkoop testified about.

The total I got under "N" for these four treatments, including placebo, is 140. Agreed? And that's what I've reflected here in my -- on my piece of paper.

MR JUSTICE BURTON: There are 38 yes's, and 102 no's makes a total of 140?

A. That's right.

MR JUSTICE BURTON: Yes.

A. Quite satisfactory. I turn you now page 2C, I've done the same thing here without using the notation "N", and under "dead" I have 26. Under "total", I have 136, a discrepancy of four. Four people have disappeared from the database or the analysis --

MR JUSTICE BURTON: 136?

A. 136 total people that are in the data.

MR NASH: Sorry to interrupt, you carry on, finish your point, please.

A. Okay, so from the previous table, which by that I mean

2A, I tried to look and see, and those: two people disappeared from the low dose, two people disappeared from the high -- from the placebo.

This to me indicates quite a number of things that have been addressed by some of the other witnesses -- experts, excuse me, they have not yet been witnesses. One, absent some other explanation, there's -- when I just look at this, there's a database problem, a data entry problem, an identification of the correct event, so that when you sought for it you get one answer that's assured and you should have a checking system that guarantees that if that happens, a red flag -- just to use Dr Goedkoop's term -- goes up, or by human inspection producing this table as evidence of any kind, submitting it to the DSMB, without doing a quality control or quality assurance on it, is -- all of these are disconcerting to me.

The same number of patients, 136, occurs below in this, with another -- which is, I believe, just a typographical error. Again, this is taken out of another document, and it was typed into this form, I believe.

MR JUSTICE BURTON: Which one are we talking about?

A. I'm sorry, my Lord. I'm looking at table 2C. it says:

"Total: 95", under drug treatment.

MR JUSTICE BURTON: Yes.
A. That number should be 99.
MR JUSTICE BURTON: That's the missing four?
A. That's the missing four, but that only takes you to 136 still. That's not the missing four. I think 95 is just a simple typographical -- and I don't ascribe that to the same level of concern as I do when the rest of these, where 136 appears in the second interim analysis database. And 136 is accurate -- those numbers that I talked to you about before that create concern are also in this BRAIN Trial second interim analysis, whatever document that is in the trial book.
MR NASH: Let's go to that to see that, Dr Simmon. It's in the core bundle at volume 2, behind tab 18.
MR JUSTICE BURTON: Can you remind me, Mr Nash, what Professor Sandercock's exhibit purports to be?
MR NASH: These are the tables which he says formed the basis of the DSMB's decision. These were the ones they focused on.
MR JUSTICE BURTON: And how do they compare with what we've got at tab 18?
MR NASH: I'm about to show your Lordship that. They are intended to be the same, and subject to the typographical error which Dr Simmon referred to, they are the same --

MR JUSTICE BURTON: Right.
MR NASH: -- with one additional point I'm going to show you.
MR JUSTICE BURTON: Thank you.
MR BEAR: Can I just clarify, I don't think this is a matter of dispute. Professor Sandercock doesn't say "these are the tables"; he says "this is the data" and then he adds some commentary to it which explains what he and his colleagues, so he says, thought was significant.
MR NASH: I wasn't trying to suggest those were the shell tables, of course, that's his reproduction of the information in the shell tables.
MR BEAR: Plus some commentary.
MR NASH: Plus some commentary.
MR JUSTICE BURTON: Yes, but isn't that what tab 18 is? Isn't that also reconstruction from the tables?
MR BEAR: Tab 18 is the figures, and Professor Sandercock effectively replicates those and then he adds some commentary just to explain to us what he derived from it.
MR JUSTICE BURTON: Yes.
MR NASH: So if we go, please, to tab 18 of core bundle 2, and go, please, to page 2761 of the document, top of the page, we have a table:
"Patients with at least one serious adverse event."

That's the equivalent of the table 2A to Sandercock.

A. Sorry, I'm looking at 2C. Yes, I believe that's correct, yes, 38 over -- and 140.

Q. That gives you the 140 figure that you mentioned. Then, if you go over the page to page 2771:

"All cause mortality to day 15."

That's the equivalent of Sandercock 2C, and you'll see there your 136 figure?

A. Correct.

Q. And you'll also see the rubric under the title:

"Note: there are four missing values for this variable."

A. I see that.

Q. And that's the four which you have identified.

A. That's the ones I've identified, and I cannot understand how this would be produced in a GCP environment, because, if you have four missing people from a table that is supposedly from the same database that you have other data generated from, something about the system you -- and I don't know where the error is, but there is something about the database, the data management, the data entry, that doesn't link these things correctly, so, when you query the database to produce a table, it can give you answers such as this that have anomalies in them that should not happen.

If you did a proper database build-up in which you tested your database against all kinds of contingencies to show that it gave the right answer, this kind of thing wouldn't happen.

Furthermore, it seems to have gone -- other than the little print-out here which nobody paid attention to, that there are four missing people -- they call them perhaps -- they call them variables -- other than that, nobody seems to mind.

I mean, this should be an alarm bell going off at the London School at the highest level, that the data we're generating, the tables that are the basis of a very, very important decision that could be made -- in fact a decision was made -- to suspend the trial was made with data that clearly had -- from a database that clearly has compliance problems. It's not compliant.

MR BEAR: I wonder if it would help if we could just be referred to the allegation that this relates to, because of course the experts have been able to look at all the unblinded material. I'm slightly at a loss to know how this fits into the latest breach notice or a pleading or anything of that kind.

MR JUSTICE BURTON: Is there anything made based on these four missing characters or any case that a database sent to the DSMB which manifestly are missing for such values

is in some way in breach of contract?
MR NASH: I don't know where we are on the pleadings in relation to that, my Lord. I'm told, not specifically, but we are of course criticising the database --
MR JUSTICE BURTON: Well, you're criticising a database on the basis of the failure to reconcile it with the TSC one, and you have various criticisms which are separately pleaded, but I wasn't conscious of any case that this database was -- to use Dr Goedkoop's legal description -- "crap", because of there being four missing values, such being apparent on the face of the documents.
MR NASH: Well, I think that's fair. I don't think it is in the pleadings as a specific point, my Lord.
MR JUSTICE BURTON: Then I don't know that it goes any further, does it?
MR BEAR: No, I suggest we don't take up further time dealing with this.
MR JUSTICE BURTON: No.
A. My Lord, may I say something?
MR JUSTICE BURTON: Yes.
A. In regard to what you just said? Since last night, or yesterday, was the first time I had a chance to see these, because of the --
MR JUSTICE BURTON: But experts have been seeing it on your

behalf, though, Dr Simmon. The criticism is not "there are four missing values", but "the defendant fell below some professional standard in doing so", and we've had experts on both sides, and neither of them have identified this failure as a failure which puts them below that standard.

I mean, that's right, isn't it? Your expert has seen this unblinded information?

MR NASH: Yes.

MR JUSTICE BURTON: The fact that there are four missing values in one table, or indeed in two tables, isn't something that she's criticised. You can't be blamed for not identifying it, but I think unless someone behind your silk is going to give an instruction for a late amendment application to make this a new part of your case, I'm not going to permit any more questioning about it.

MR NASH: I had reached the end of the point anyway, my Lord, but we'll reflected on that, of course.

Finally, it's been suggested, Dr Simmon, that you are now in an unblinded state as a result of having seen the Sandercock schedules. What's your view of that?

A. I have several views. I share Professor Roberts' view that we are both now partially unblinded. That is, we can't link patients with the information we've seen.

We see a picture at a point in time when a certain number of patients had treatment or not, and we see both the safety and outcome measures for that, but, as you add more data on top of those patients, they will, in essence -- we won't understand what happened to those as individuals because of the degree of unblinding. So that's the first point.

Secondly, according to the FDA regulations -- excuse me, guidelines on blinding, they talk about it in a document that was referenced by Dr Roberts and also summarised in his witness statement 3 at paragraph 37, where he describes what the effects of unblinding are, and they're really on -- the concern in blinding reflects whether or not a person who is treating the patient, the patient themselves, because he is a double blind, the person treating the patient, the person who is collecting and analysing the data would have a bias because they know the treatment.

In this clinical trial, that is not Xytis or any employee of Xytis, including me. That is the London School of Hygiene, which is collecting and analysing the data.

So unblinding me, or any employee of Xytis, at this point in time is irrelevant according to the guidelines cited by Dr Roberts, because we are not collecting or

analysing the data.

So we can't influence the -- for example, and a concern that I have is that the London School people who have been unblinded are involved in the cleaning process, and their queries or failure to make queries could affect the quality of that data because they had been unblinded, and have seemed to have reached a conclusion about the safety or non-safety of Anatibant.

MR NASH: Thank you, Dr Simmon. I have no further questions in chief.

Cross-examination by MR BEAR

MR BEAR: Just on this last point, your company, Xytis, hires the CRAs in this trial, doesn't it?

A. I'm sorry, is that a question?

Q. Yes.

A. Hired a CRO?

Q. No, the CRAs, the monitors?

A. CRA? We contract with individuals in a variety of countries to perform CRA services in those countries under the direction, supervision and reporting to -- inputting the data to the London School of Hygiene and Tropical Medicine, that is correct, but we contracted with the individuals.

Q. One example is a lady called Eva Cachin, C-A-C-H-I-N, is

that right?
A. Eva is a CRA and an employee of Xytis.
Q. Exactly, so she is involved, I think, in the Czech Republic, isn't she?
A. She is involved in the Czech Republic, yes.
Q. And she is supposed to collect the data and do the first entry of the data, correct?
A. That is correct.
Q. So she reports to Mr Furcha?
A. That is correct.
Q. And he reports to you?
A. That is correct, and I report to the board.
Q. Indeed. So at one remove from you is Ms Cachin who is involved in filling in the forms and entering the data, is that correct?
A. That is correct.
Q. And so it means that at one -- if you are unblinded, at one remove from you there is an employee of Xytis who is engaged in data collection, correct?
A. Let me explain an answer to Mr Bear's -- am I pronouncing your name correctly?
Q. Yes.
A. In a clinical trial run by a pharmaceutical company, a big pharmaceutical company -- not a Xytis, a Pfizer or Merck -- employees of the company perform the services,

for the most part, that the London School is performing for Xytis, that is, people who are employees of the company collect and analyse and clean and do all those things with the data.

They have a Chinese wall built with one or more people behind that wall who is actually unblinded to the code of the trial.

So having a person within your company -- whoever that person reports to -- is not the issue; the question is are they exposed to unblinded data, and Ms Cachin has not been exposed to unblinded data. Mr Furcha, to the best of my knowledge, has not been exposed to unblinded data. Only I have, as a CEO of the company.

At this point in time I believe that's correct.

Q. I understand. I was --

A. So the fact that there's a reporting relationship, of course there will be, we are a very small company, but she has not been unblinded in any way to the data.

Q. It's simply this -- sorry, I'll try call you Dr Simmon, but if I slip into Mr, please forgive me. It's just this, Dr Simmon: you seem to be drawing a comparison at page 174 of the computer transcript -- I know you don't have it -- but you said this:

"Unblinding me or any employee of Xytis at this point in time is irrelevant according to the guidelines

cited by Dr Roberts, because we are not collecting or analysing the data.

"So we can't influence the [and then a break] -- for example, and a concern that I have is that the London School people ..."

A. I sit corrected, I'm sorry.

Q. You agree with the point I make?

A. I do, indeed.

Q. Thank you very much.

Then we can move on. You joined Xytis as CEO in late 2006. Have I got that right?

A. 20th November, 2006, yes.

Q. At that stage, the Anatibant trial was already well into preparation?

A. That is correct.

Q. LSHTM had been recruited and contractually engaged some months before?

A. That is correct.

Q. By your predecessor, Dr Tschollar?

A. Dr Bernard Tschollar, yes, that is correct.

Q. Is it fair to say that in your seven witness statements you don't give any description as to the steps that you took after you joined Xytis to familiarise yourself with the BRAIN Trial and the work that LSHTM was doing?

A. I believe I referred to them in my witness statement

saying that when I first came into the company -- indirectly, I refer to them indirectly -- by saying when I first came into the company there were some financial issues that -- the company appeared that it would run out of money soon, and I needed to raise money. That was a big priority.

Going through the process of terminating Dr Tschollar by the end of January was distracting, as we did not have a CFO at the time and I was acting as Chief Financial Officer of the company at the time.

The trial at that point, in the first quarter, had not enrolled its first patient. As the trial began to enroll patients, my more immediate concern -- and even before it enrolled the first patient, the board had certain expectations about when the first patient would get enrolled, and how fast enrolment would go.

So my focus was on a number of different things, and I did not thoroughly immerse myself in the details of the BRAIN Trial initially. That is correct if that's your question that I've answered.

Q. It sounds like you were trying to keep the company afloat.

A. I was at that time until I raised an additional $15 million in June -- July/August of 2007.

Q. So the fund-raising exercise began at the start of 2007

and was complete by July/August?
A. It meant that --
Q. Just for the record, could you say "yes", if you agree?
A. Yes, I agree.
Q. Thank you. Go on, you were about to say, I interrupted you?
A. No, I think you got it right.
Q. Okay.
A. It began the day I came to the company, but as a practical matter, it began in January 2007.
Q. Without going into specifics, did you raise funds from the entities who have representatives on the board of directors?
A. That is correct.
Q. So, for example, Mr Flugal represents Sanderling, is that right?
A. Dr Flugal.
Q. Dr Flugal, I'm sorry?
A. PhD.
Q. Very well, many titles important, I'm just plain Mr, but Dr Flugal represents a fund called Sanderling, is that right?
A. Sanderling Ventures.
Q. There's a director called, I assume Monsieur, or perhaps it's Dr Guerin?

A. I don't think he was a doctor, but Herve Guerin had been the COO of the combined firm of Sanofi Synthelabo. I believe he was with Synthelabo and then when the two firms merged he became chief operating officer before he retired. So he has big pharm experience, medium pharm experience.

Q. There are other directors who represent other investing groups?

A. Yes, just to be clear, Monsieur Guerin did not represent an investor group; he was what we call an independent director, and he was initially chairman, when I came to the company. He stepped down from that position, and the board elected me chairman, and subsequently he retired from the board during the past year, several months ago.

Q. I'm talking about someone called Herve Guerin, G-U-E-R-I-N?

A. Yes, correct, the same man.

Q. Was he not a board member in November?

A. When I came to the company?

Q. No, November 2007.

A. 2007, he was on the board of directors in 2007, that is correct.

Q. So are you saying he's now left, or --

A. I am saying that.

Q. And when exactly did he leave?
A. In the last two months.
Q. You've told us that you didn't immerse yourself in the detail. I don't want to trap you, just tell me to the best of your recollection, do you think you looked at the protocol for the BRAIN Trial?
A. I had read the protocol actually before I accepted the position at Xytis under a confidentiality agreement as part of my diligence before I accepted the job.
Q. Right. Okay, so that would have been some time in, when, October or something?
A. September -- August/September/October timeframe when I was being interviewed, yes.
Q. Can you recall whether it was the approved protocol or just a draft at that stage?
A. I believed that it was, although as you know there have been protocol amendments so I was looking at a document which I don't recall if it had a version on it, et cetera, so -- to the best of my belief, it was the approved protocol.
Q. Did you appreciate that the CTSA was in agreement for LSHTM to run the trial under the terms of the protocol?
A. I did not believe during my diligence -- I do not -- I specifically remember reading the protocol, but not the CTSA. So some time later I read that.

Q. Yes, I should have been more clear in the timeframe and I apologise. Did you appreciate by, say, the spring of 2007 -- so after you'd been in post for three or four months -- that the CTSA was in agreement to run the trial under the terms of the protocol?

A. I would say very early, even at the very end of 2006 or early 2007. In fact, in reflection, Dr Roberts -- or Professor Roberts, whichever you prefer -- visited Xytis to talk about the clinical trial to our board. That might have been in November 2006 or January 2007, I can't remember which.

So I did appreciate the relationship, if not the complete details of the contract.

Q. Just so that we're clear, the point I'm on is this: was it your understanding that the CTSA was in agreement to run the trial according to the terms of the protocol, in line with the protocol?

A. Yes.

Q. Now, could you take a bundle which is called core bundle-volume 1? Could it be given to you, please? Core 1, tab 3.

This is the protocol, Dr Simmon.

A. Yes, it is.

Q. What I'd like to you do, there are some page numbers stamped at the very bottom of the page, and if you could

go to 322?
A. Yes, sir.
Q. And section 17 of the protocol is headed:
"Study schedule", isn't it?
A. Yes, sir.
Q. Do you agree that that runs from an anticipated start in November 2006 to an end in August/September 2008?
A. I agree that is what is said, and when we say "start of the trial", that word has some elasticity to it as you might imagine. In some language, the trial started when the contract was signed, or the protocol was approved, or it could have been the enrollment of the first patient.
Q. If we look at the second line, Dr Simmon:
"First patient treated ..."
A. First patient treated November 1, there it is. So that is more specific.
Q. That clears up the ambiguity, doesn't it?
A. Thank you.
Q. In order to start a trial, you obviously need regulatory approval in whichever country is involved, correct?
A. In all the countries where you intend to enroll patients?
Q. Yes, each country has its own regulator?
A. Yes.

Q. So the fact that I might have a licence in England doesn't mean I can do anything in India, for example?
A. Absolutely correct.
Q. Now, this timeframe here shows a period of approximately 19, 20 months, something like that?
A. I'm not going to do the math, I'll take your math.
Q. A little bit short of two years.
A. Fine.
Q. Did you understand, when you looked at the protocol and begun to familiarise yourself with the trial as you moved into your new CEO role, did you understand that this would have been the party's expectation about the rate of recruitment?
A. Clearly, it was the parties who were party to this at the time they signed it in 2006, I believe August, yes. I wasn't party to it.
Q. No.
A. And I would point out, Mr Bear, that there is inherently a problem in this last patient treated. Xytis has an obligation from its licensor -- another agreement I had to learn about -- with a company called Solvey, formerly Fournier, which requires that we start a phase 3 study by mid-2009, and this makes it somewhat difficult to make that timeline for a variety of reasons.
Q. So you're saying your option lapses, does it, in effect?

I'm using the words loosely, but --

A. Using the word loosely, that's correct. Xytis's right to continue using the drug could expire prior to the start of the phase 3 trial.

Q. So far as my clients, LSHTM, are concerned, they've never seen that document, have they?

A. I don't know.

Q. It's not been disclosed in these proceedings, for example.

A. You're asking me -- I don't know if Dr Tschollar saw it.

Q. To your knowledge have they ever seen it?

A. That's what I said, I don't know, that's my knowledge, I either know or don't know.

Q. Coming back to this, just tell me if you agree or disagree: this would have been the expectation of LSHTM for the recruitment programme of the trial, this timeframe, do you agree?

A. Yes, sir.

Q. Could you be provided with a bundle which is marked:

"Claimant's further supplemental disclosure 1"

please?

A. Are we done with this for the moment, or --

Q. Yes, if you could just put it to one side without folding it away completely. We're going to look at page 39.

If we could look, please, at page 39, at the bottom of the page again, is this a presentation that you were responsible for to the board of directors on March 26th?

A. Just a second, please?

Q. Yes, certainly.

A. I'm having a little struggle.

Q. You might want to unclip it.

Sorry, I'll put the question again, Dr Simmon. Is this a presentation that you had responsibility for to the board of directors of Xytis on 26th march?

A. Yes.

Q. We don't have it all because your solicitors have decided which the relevant pages are, but if we look at the next page, which is page 3 of the slides --

A. Would you give me a page?

Q. 40.

A. 40?

Q. Yes.

A. Thank you.

Q. So this is the agenda, operations, and then second line, Anatibant enrollment.

Then go forward to 46, if you would.

A. Yes.

Q. Did you prepare this chart?

A. No.

Q. Did someone prepare it on your instructions?
A. Mr Rowland Furcha prepared this chart.
Q. But did you approve it? He is not a director, is he?
A. No, but when you are running a company, as I am, you ask people to make documents for you, and you use them based on your belief that they have provided you with the correct information.
Q. Fair enough.
A. In that sense, I accepted his projection.
Q. You would have looked at it before you took it to the board, obviously, the board meeting would not have been the first time, correct?
A. Yes, sir.
Q. Looking at this, what we've got with the diamonds, ie with the long line, is what is described in the heading as the "planned patient numbers", do you see that?
A. Yes, I do.
Q. And that, I suggest, shows a recruitment ending with 400 patients, being the top line, some time in February of 2008. Have I read this correctly?
A. That is correct.
Q. So that shows recruitment ending some six months earlier than the protocol, correct?
A. Correct.
Q. Why was that?

A. We believe that the -- as I indicated before, it would be necessary -- desirable and in fact contractually more than desirable, potentially necessary, to accelerate our enrollment over the projection that was in the London School. We'd had discussions with them about this and how to do it.

We added several sites, I believe in Estonia, and were intending to add some sites in Latvia ourselves as part of the trial, which was permitted under the -- both the protocol and the CTSA, to achieve this.

I might add, if I may --

MR JUSTICE BURTON: Yes.

A. -- that, a practical matter here, which I've alluded to, but to be clear, Xytis may have, at the time Dr Tschollar was CEO, thought -- that is, Dr Tschollar may have thought -- that it would be possible to run from a phase 2 immediately into a phase 3 trial. That's not a practical matter for the reason that such phase 3 trial would require, we estimate, at least $50 million, but we don't have a real number, because the trial hasn't been designed.

MR BEAR: There would have to be a fresh round of investment, as it were?

A. No, there would not be a fresh round of investments because I do not believe any investors would put forth

that type of money. So what would happen to -- it's more accurately stated -- it's fresh money, but the source of that money would be a pharmaceutical company.

So what we would have to do is take the data from the phase 2 trial, which would have to be ICH-GCP compliant, to the fullest extent, because we would then take this around to pharmaceutical companies, show them our data, assuming there was a signal of efficacy.

If this drug did not show at least a trend or a blip, or something, no pharmaceutical company would invest 50 or 100 million, or whatever the number is, to run a phase 3 trial.

Phase 2 trials, unlike what is stated in Professor Roberts' witness statement -- I don't remember which one -- are not run for the purpose of safety only. That's included. Safety is always included. Every --

Q. Can I just interrupt you? I'm going to be covering these topics with you, so --

A. I will abbreviate my response to you, which is what you wanted, really, to abbreviate it?

Q. Yes.

A. So, as a practical matter, we needed to do certain things, and we talked about them, and one was increasing the rates of enrollment by the methods --

Q. Let's take it by stages.

A. Sure.
Q. The point that I'm on is: here we are in March, and you are trying to raise money to keep the company afloat, correct?
A. Yes.
Q. And you are holding out to the directors who also represent investors, a planned recruitment programme ending in February 2008, correct?
A. That is what I believed to be the case at the time, yes.
Q. And it's what you held out to those who were your investors and were going to invest some more, correct?
A. To my board of directors.
Q. Yes, who also represent your investors?
A. At this point, they're all investors, so they're the same thing. It's a practical matter.
Q. Yes. And it was inconsistent with, because it was much shorter than, the rate which was implicit in the protocol, correct?
A. That is correct, and for the reasons that I told you, we thought we could achieve a faster rate than the protocol because we were permitted to and were adding centres independently of those that had contracted directly with the London School. They did eventually contract with the London School, but we were the ones who recruited them.

Q. Of course.
A. So the dynamics were changing. A lot of things changed here.
Q. I understand that.
Now, did you tell LSHTM at this time that you were going to try and take steps to boost recruitment in this way?
A. That was an open discussion. I wasn't privy to all the details of it. But to my knowledge the fact that we were talking to places -- sites, potential sites, in places like Estonia and Latvia was known -- to my knowledge was known -- to the London School, because ultimately they contracted with those sites.
Q. My question, though, was whether you told LSHTM at this time -- to your knowledge -- that Xytis was going to try to take steps to boost recruitment and finish recruitment by February 2008?
A. Whether I specifically mentioned that date with that precision, I don't recall.
Q. What about did you tell them that you wanted to speed recruitment up very considerably from what was in the protocol?
A. I do recall, and I cannot place times and dates on this, I can look to email references that there were discussions between and among Mr Furcha at that time.

I --
Q. I'm asking about your knowledge, Dr Simmon.
A. I don't remember when it happened. That's simple. But, yes, we did communicate it. I don't remember when.
Q. If we could go forward in the bundle that we're in, "Claimant's further supplemental disclosure", could we go to page 80 which is the board of directors' meeting on June 14th?
A. Yes, sir.
Q. If you could look, please, at page 87? This is the same chart, isn't it, with the addition of some data at the bottom?
A. With that caveat, it is.
Q. The same planned rate, and obviously we've got a couple of months more actual added, or three months more, correct?
A. Yes, sir.
Q. What this chart shows is that the planned rate according to your plan should have been 110 by mid-June, but the actual rate was about 40. That's what it shows, doesn't it?
A. It shows that, but realising that what Mr Furcha was asked to do was give us a timeline that will give us a February 2008, more or less, completion, and he complied with those instructions with this chart,

I believe I may have said first quarter of 2008, what have you, and this then informs the board that we're not -- we're not achieving a rate up to this point in time that would allow completion by that first quarter of 2008.

So it's information to the board about the fact that our projection may be overly optimistic.

Q. I suggest it's a bit more than that, isn't it? Weren't you, at least by implication, criticising LSHTM for failing to meet the planned figure?

A. No, sir.

Q. Do you think a member of the board of directors could have come away with that impression?

A. These are gentlemen who are professionals, they come away with various impressions. I do not query them to find out their impressions.

If I were to take this and criticise somebody, it might be Dr Simmon, for giving us a projection that's kind of unrealistic. That would be an impression, if I was a board member, you'd better get your numbers a little better because you're not making them.

Q. You see, I suggest that there was criticism that you were directing at this time to LSHTM. Would that be fair?

A. That I was directing?

Q. At this time, mid-June 2007, you were directing criticism to LSHTM in relation to the rate of recruitment. Is that a fair comment that I've made or not?

A. I would recast that to say that we were having discussions with them, we would like to accelerate, we talked with them, we met with them and talked about how this could go about, there are minutes of that meeting in which that discussion is indicated. We talked as collaborators about how to increase this and whether or not it could be done as a practical matter. We offered to provide additional assistance, if I recall correctly, if necessary, to achieve that.

Q. All right, could you be given chronological bundle 6, please? Page 1656.

A. I am on that page.

Q. Thank you very much. This is your letter to Professor Roberts of 12th June, isn't it?

A. Yes, it is.

Q. Is this the first letter you'd ever written him?

A. I do not recall.

Q. I may have missed something, but in the bundle I couldn't see any others prior --

A. You've asked me a question. The evidence that you've just stated is, in the bundle we don't see any previous

ones, I assume that's what you're saying. I don't recall if I wrote him one and it didn't end up in there somehow --

Q. Okay --

A. -- but we had communicated on several occasions.

Q. Let's just remind ourselves of the text of this letter.

A. I think that's more important.

Q. "Xytis ..."

Well, his Lordship will decide at the end of the trial what's important.

"Xytis recently received the third LSHTM invoice for £282,795. Before remitting payment for this invoice, we believe it is important that TCC ..."

That means LSHTM, doesn't it?

A. Yes, sir.

Q. "... and Xytis reach agreement on a number of extremely important issues."

Just pausing there, you're saying: before we can put the money on the table, Ian, you have got to agree the following, correct?

A. Well, when you reach agreement, it doesn't mean "you do what I tell you"; it means: we, grown men, discuss, come to an agreement, that's what it means.

Q. Without that agreement, you weren't going to pay, that's what you're saying?

A. It says "before remitting this invoice", that is correct.
Q. Now, you then go on to talk about the nature of the contract and whether it's fixed price or cost.
A. Which had an important bearing on whether or not that invoice was actually valid.
Q. I understand that that's your case. We're not dealing with that in this legal trial, you understand that, don't you?
A. I do.
Q. And --
A. And that's why I don't think it should be -- I should be questioned on it at this point.
MR JUSTICE BURTON: Move on. Let's come on to the next paragraph.
MR BEAR: That's why I'm moving on.
"Second, and much more troubling is the poor progress in enrolling patients. I, along with our board of directors, am understandably concerned with the current recruitment rate. To date, only 38 patients have been enrolled in 15 of the 17 sites initiated. Most tragically, only 6 of the initiated sites are enrolling patients. Extrapolating current performance, 14 patients per month in May 2007, we would not complete recruitment until August 2009. A doubling of

recruitment would see completion of the trial in July 2008 coinciding with the study drug expiry."

Just pausing there, that is, I suggest, clear criticism of LSHTM?

A. However, it's explained in August 2009, which is substantially later than the date we referred to before in the protocol.

Q. Sorry, could you just focus on the question. Do you agree -- I think you do, but tell me if you don't -- that this is criticism that you're making of LSHTM?

A. I am pointing out in a critical fashion -- if that helps you -- that the enrollment rate at that time would fall behind --

MR JUSTICE BURTON: That suggests it's their fault that the recruitment has fallen behind?

A. Yes, sir, and there was a reason for that.

MR JUSTICE BURTON: We don't need to go into the detail at the moment. But you are making a criticism of the defendants in relation to delay in recruitment, is that right?

A. Yes, sir.

MR BEAR: Now, at this stage I suggest LSHTM were never aware of your expectations for the planned rate of recruitment. That's correct, isn't it?

A. I don't know if that is correct or not, because --

Q. Are you able to contradict it? Let's put it like that.
A. I am not able to contradict it.
Q. So when you wrote this letter, it must also follow that you had no information to suggest to you that LSHTM were aware that you wanted to march to a different and faster beat, is that correct?
A. I disagree with that.
Q. So you don't have information now suggesting that they knew you wanted to go faster, but you did have information in June last year, is that your evidence?
A. I know there were discussions that were ongoing between Mr Furcha and primarily Ms Shakur about enrollment. You're asking me details of that that -- I don't know what the details of those discussions.
MR JUSTICE BURTON: The protocol provided for when?
MR BEAR: The protocol provided, if it started on 1st November, ending in August/September 2008.
MR JUSTICE BURTON: So that was the period which your clients could be said to have been expecting?
MR BEAR: Exactly.
MR JUSTICE BURTON: Against that background, you're making this criticism. Do you think that was a fair criticism or not?
A. Yes, because my projection, my Lord, says that they wouldn't finish until 2009.

MR JUSTICE BURTON: Right.
A. That's at that rate.
MR BEAR: If we look at page 225 in "Claimant's further supplemental disclosure 1" -- this is the one that had the board presentations in it.
A. I'm back to it.
Q. This is from a board presentation that's much more recent, which we can see from the bottom left of the page, 8th January this year, 2008?
A. Correct.
Q. And here we've got the graph done differently.
Now, this shows, doesn't it, recruitment ending in May 2008, is that right?
A. Correct.
Q. 2009, sorry.
A. No, I think that's 2008.
Q. So what's happened is that it's been pushed back, is that right?
A. I believe what Mr Furcha did precisely here, the previous chart had started with enrolment in sort of February or something, this chart was, as you said, pushed back three or four months, so from February to May.
Q. Yes.
A. Three months -- three or four months.

Q. You see, if we look at the figures for June on this chart, page 225, we can see that the --
A. For June? Looking at the figures for June, I've got it.
Q. We see the first June -- well, the only June, so the diamond again is the planned rate, correct?
A. Right.
Q. And that shows something like 40 patients, correct?
A. I'd say maybe -- oh, it's middle of the -- I'm not sure how he did these charts, whether it's the middle of the month or the 1st, it's hard for me to read, but it looks like, to answer your question as best I can, the fourth set almost overlap at 50 patients. Do you want to go back to May? They overlap at around 35 or 40. There's a solid number behind these. I don't remember the number.
Q. Sure. The point I was making is that the planned patients are 40 or maybe a little over, and the recruited, which is the actual, the square, is actually a little above, isn't it?
A. It's above it, so, in your previous question, you asked me if I was criticising LSHTM or Vince. Now I'm congratulating both of us. We're ahead of the new schedule, the revised schedule.
Q. If you push the -- I'm just using this to illustrate the point, Dr Simmon. If you push back the end date just

to May 2008, then you can see that on that sort of projection, LSHTM was around or perhaps even slightly ahead of the projected rate of recruitment --

A. At the beginning of 2008, last month.

Q. Sorry, if you let me finish. If you push back the eventual point to May 2008, then on those figures, LSHTM as at mid-June, was in line with what would have been expected, do you agree?

A. Under the new projections, that is correct.

Q. Under those projections. So it's not a case of LSHTM somehow recruiting at a rate which would have led one to wait until the middle of 2009, is it?

A. Well, you're taking a time point substantially later and asking me if anything changed, and this chart shows a lot has changed. The projection -- and the recruitment, we were all very pleased to see 60 people come in in August. So things had changed, yes. We have actual and projection, and both had changed on this chart from the previous chart.

MR JUSTICE BURTON: Would that be a convenient moment?

MR BEAR: It would be convenient point, thank you.

MR JUSTICE BURTON: Thank you very much indeed. You mustn't talk about your evidence now while you are in the witness-box.

A. I understand that, my Lord.

MR JUSTICE BURTON: And I will look forward to seeing you back again at 10.30 in the morning.

Could we have tomorrow morning (a) an agreement or at any rate an isolated disagreement on confidentiality, and a timescale for witnesses, a schedule of witnesses?

MR BEAR: Yes.

MR JUSTICE BURTON: And again, we'll see what it looks like and if it's pessimistic don't worry about it, we'll see what we can do.

(4.25 pm)

(The court adjourned until 10.30 am the following day)

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