**REPORT ON PROCEEDINGS BEFORE**

# SELECT COMMITTEE ON OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW

## PRIVATE BRIEFING

**PUBLISHED BY RESOLUTION OF THE COMMITTEE ON 29 NOVEMBER 2016**

**At Macquarie Room, Parliament House, Sydney on Monday, 31 October 2016**

**The Committee met at 9:00 am**

**PRESENT**

The Hon. P. Green (Chair)

Mr J. Buckingham
The Hon. C. Houssos
The Hon. T. Khan
The Hon. N. Maclaren-Jones
The Hon. W. Secord
The Hon. B. Taylor (Deputy Chair)

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**DR DAVID ROBERT BELL,** Senior Medical Oncologist, Northern Cancer Institute, sworn and examined

**The CHAIR:** Dr Bell, thank you for coming in today. You would well know that we are undertaking an inquiry into off-protocol chemotherapy. Your presentation today is to help the Committee to quickly get on board. We do not have a great deal of experience in these matters, especially compared to the years of experience that you and many of your colleagues have. We are hoping to find out about world's best practice, Australian best practice and, of course, best practice in New South Wales. Could you also give the Committee some detail on off-protocol use around the world, because I know in the United States of America it has been taking place for some time. It would be helpful if you are able to provide a little of the history of that. We are at your disposal.

**Dr BELL:** Thank you. It is a pleasure to be here and help you understand the complexity of dealing with cancer patients. We are dealing with people who clearly have significant physical, emotional, psychological and spiritual needs, and not only them but their carers, relatives and friends. It is becoming increasingly complex because there are a great many more options available in 2016 than even several years ago. And, of course, the press seems to be full of the latest breakthrough "which is going to cure cancer in the next six months" every few weeks. Unfortunately that gives people a lot of false hope. One of our roles as oncologists is to help people navigate this enormous maze of material that is out there in terms of treatment options.

Whilst I will be focusing predominantly on chemotherapy, I just want to touch on the other aspects. We are not "chemotherapists". We are physicians who treat patients who suffer with malignant disease which for many patients will be terminal—I do not like that word but it means "end of life". I thought I would give you a brief overview about how we dose chemotherapy. Chemotherapy works basically by targeting dividing cells in a number of different ways and through a number of different mechanisms. Because many of our normal tissues, such as our bone marrow, have rapidly dividing cells they can be affected by chemotherapy too. Most patients become pretty quickly aware that their bone marrow can be suppressed by chemotherapy. They are all very aware of things like losing their hair. They are probably less aware of things like the diarrhoea that can occur because they get inflammation of the bowel.

One of the problems we have is that we are using very potent drugs with what we call a very narrow therapeutic window. In other words, the difference between the dose that a normal cell will survive and the dose required to kill the cancer cell is actually very small. If you go on either side of that you will either over-treat and increase not only toxicity but potentially death and if you go below that you potentially reduce the efficacy. So patients need to be aware that when they are undertaking these therapies they do have a risk of infection, diarrhoea and, unfortunately, sometimes death from chemotherapy.

One of the difficulties at the beginning is that we do not really understand each individual in terms of their own metabolism and how they are going to handle the drug. We are all familiar with people who can, say, have penicillin for an infection but other people are, of course, quite allergic to it. You do not know until you have a drug in your system how you are going to tolerate it—and nor does your prescribing clinician. Most of our drugs in chemotherapy are metabolised by the liver and a smaller number are excreted by the kidney. That means if there is any renal or liver impairment there may be some problem in handling that drug. There are also differences between patients and their ability to clear the drugs. These are definitely related to genetic factors. If we could do a DNA profile of everybody we may be able to tailor chemotherapy even more effectively and efficiently. Slower clearance of drugs due to kidney and particularly liver problems could lead to increased toxicity.

What are the end points that we use? I guess one of the end points that we use predominantly—and it is a very fixed end point, of course—is survival: Are patients being treated with these drugs living longer than patients who would not have been treated? Other end points that we look at are things like response rate: How many patients receiving this chemotherapy get a tumour regression? We look for things called progression-free survival. If you are on the chemotherapy, how long do you get before your disease starts to progress compared to another group of patients where they may not receive the same therapy?

There are a number of different end points. Some of them, I feel, are a little fuzzy. Overall survival is clearly a very defined end point. The most important thing from a patient's perspective is—and I apologise for this term because it tends to be a bit overdone—quality of life. That is indeed an end point in its own right, and particularly when you are dealing with a non-curative therapy. Patients do not necessarily want to go through

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increased toxicity for a minimal increase in survival, which could be on average two or three months, at the expense of their quality of life. That is something we have to bear in mind. I will amplify that a little later.

Importantly, how do we determine the first dose of chemotherapy to give a patient? This is worked out through a number of clinical trial mechanisms. We have phase one clinical trials, which are effectively dose finding. The patients are human guinea pigs. They volunteer to be in a trial so that we can understand how the drug is metabolised and what is the maximum tolerated dose. They may or may not get some benefit from it. They certainly provide enormous benefit, through their generous support of these trials, for the next phase of testing which is phase two. Phase two trials use the drug at the dose that has been selected in phase one, in what we call the validation study.

**The Hon. WALT SECORD:** Excuse me, Chair, may members ask questions?

**The CHAIR:** Yes, please do.

**Dr BELL:** I would be very happy to answer questions.

**The Hon. WALT SECORD:** May I ask a clarifying question? Do phase one trials relate to individual patients? If I were receiving chemotherapy, would you trial it on me first to see how I reacted?

**Dr BELL:** That is a very good question. Thank you for asking it. A phase one trial would involve patients with a malignancy who have perhaps failed all the traditional treatments. The approach would be, "There is a new drug available. Do you want to be included in the trial?" That may be for any cancer. They will go in at a low dose. Patients are accrued at that dose and then evaluated to determine the toxicity and tolerability. Then we move up to the next dose level and so on.

**The Hon. WALT SECORD:** Do you undergo this process when someone is already taking an established drug like Carboplatin?

**Dr BELL:** No, this is to establish the efficacy of a drug before it moves to phase two.

**The Hon. WALT SECORD:** Thank you. You have answered my question.

**Dr BELL:** So these patients truly are very generous guinea pigs.

**The Hon. COURTNEY HOUSSOS:** Is patient consent to be part of a trial different from the consent that would be required for traditional chemotherapy treatment?

**Dr BELL:** Absolutely. In a trial, patients undergo treatment with an unproven product—unproven in terms of both its efficacy and, importantly, its toxicity. Those patients receive a very complex consent form. It is very difficult to explain to them what they may experience because it is a brand-new drug. Normal chemotherapy consent forms relate to drugs that are currently on the market. We know pretty well what the possible side effects are going to be, so they are consenting with a little more information but they do not know how they will respond or react to it until they have it.

**The CHAIR:** Dr Bell, for someone with pretty serious cancer, what would be the expectation about full disclosure of all treatments? Would you expect off-protocol chemotherapy treatment to be included in a full disclosure discussion of all treatments or do doctors focus on the first stage, trying to knock over the cancer, and consider that there is no need to talk about the second stage? I am referring to informed consent.

**Dr BELL:** That may be amplified in some of the subsequent slides. At the moment I am talking about how we develop a drug to the point that you are asking about, in terms of informed consent and off-protocol prescribing. I have here some very interesting Sydney information that is peer reviewed and published. I have a copy for each member.

**The CHAIR:** That is fantastic.

**Dr BELL:** The phase three study is where you are looking at a particular tumour type—for instance, breast cancer or bowel cancer—and validating that new product against what would be regarded as best practice at the time. This is a very rigorous process for evaluating not just efficacy but, very importantly, toxicity.

**The Hon. TREVOR KHAN:** What sort of time frame is involved in the phase one, phase two and phase three trials?

**Dr BELL:** Phase one and phase two can generally take a couple of years. Phase three trials these days tend to be international, so we accrue information very rapidly, particularly on common tumour types, but it can take several years to evaluate the information and work out whether it becomes the next stage in best practice.

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There is a lot of misinformation out there about chemotherapy dosing. It can be given as a milligram per kilogram, according to how big you are. Most commonly we use what is called body surface area, which is a calculation of your surface area using a formula relating to weight and height. It is milligrams per metre squared. We use fixed dosing. Many of the newer so-called targeted agents, which target a particular molecular problem in the cell, are given in fixed doses, no matter whether you are 200 kilograms or 50 kilograms.

**The Hon. TREVOR KHAN:** Sorry, I was concentrating on the slide. Would you repeat the last part?

**Dr BELL:** Many of our newer drugs, the so-called molecularly targeted agents, are targeting a particular molecular problem in the cell. That is the way in which they have anti-tumour efficacy. They are generally given as a fixed dose. Sometimes there are a range of doses, so you can dose reduce because of toxicity, but you would normally start with a fixed dose, no matter whether the patient was 200 kilograms or 50 kilograms.

**The Hon. WALT SECORD:** That is not Carboplatin, though.

**Dr BELL:** No, that is not Carboplatin.

**The CHAIR:** This is a general overview first.

**Dr BELL:** This is a general overview. You are a point ahead of me. Carboplatin is the next area under the curve.

**The Hon. NATASHA MACLAREN-JONES:** Does the dosing vary from State to State and country to country?

**Dr BELL:** No. The fixed dosing would be—

**The Hon. NATASHA MACLAREN-JONES:** I mean across all of them, so one might use milligrams to kilograms and another might use fixed dosing. Can it vary across States and countries?

**Dr BELL:** It should not vary across States because the drugs on the PBS—particularly the PBS-listed drugs—the manufacturer's instructions for dosing are very clear.

**The CHAIR:** What about America and Australia?

**Dr BELL:** It is identical. We are talking about drugs that are available in both countries, apart from a very small number of new drugs that may be approved by the FDA [Food and Drug Administration] before they are approved by the TGA [Therapeutic Goods Administration].

**The CHAIR:** Okay.

**Dr BELL:** Then we come to the concept of area under the curve, which is just a plasma concentration over time related to renal function; hence your question about carboplatin.

**Mr JEREMY BUCKINGHAM:** The cisplatin uses the BSA [body surface area].

**Dr BELL:** Yes.

**Mr JEREMY BUCKINGHAM:** Carboplatin uses—

**Dr BELL:** It uses "area under curve".

**Mr JEREMY BUCKINGHAM:** Why the difference?

**Dr BELL:** Toxicity and efficacy.

**The Hon. COURTNEY HOUSSOS:** Before you go on, can you say which one uses which?

**Dr BELL:** For cisplatin we use milligrams per metre squared. When carboplatin was first developed—it was developed by a pharmacologist in London—it was a dose in milligrams per metre squared. Some other pharmacologists realised that perhaps a better way of dosing might be area under the curve if you are using it as a chemotherapeutic agent, not necessarily in its other role as a radiation sensitiser. So we would not work out area under the curve. That is a function of your age, whether you are male or female, your body weight and renal function. It gives a plasma concentration over time. I hope that is clear.

**The CHAIR:** We will not all come out doctors but you have been incredibly helpful.

**Dr BELL:** I am sorry if I slip into jargon.

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**The CHAIR:** No, your evidence is great.

**Dr BELL:** I am happy to slow down and explain things. I do not want to assume knowledge.

**The CHAIR:** Dr Bell, three of us are nurses and—

**Dr BELL:** Excellent; so is my son.

**The CHAIR:** Long live the nurses.

**The Hon. BRONNIE TAYLOR:** I like that.

**Dr BELL:** Yes, good for them. They have been of the greatest assistance in my career, I must say.

**The CHAIR:** We will note that on the record.

**Dr BELL:** I often say to my trainees, "Listen to the nurses because they have been there a lot longer than you." One of the other factors in terms of chemotherapy dosing that we need to bear in mind is age. Clearly, a 30-year-old patient is likely to tolerate treatment far better than a 90-year-old patient. Comorbidity is another factor. Patients may have other issues such as hypertension, diabetes, cardiovascular disease, a range of other things, leading to their being suboptimal patients to receive chemotherapy in what we would regard as full dosing. The extent of the disease has an impact, too. A patient who is—to use the horrible colloquial terminology—riddled with cancer, who has a huge bulk of disease, is less likely to tolerate chemotherapy well at a standard dose. A patient who has a minimal bulk of disease will probably tolerate it quite well, other factors being equal.

Then we come to this concept of "performance status". Performance status is a terminology we use a lot in oncology. In simple terms it is just asking a patient, "How are you doing?" "How well do you feel?" We use, most commonly, the ECOG performance status. That is the Eastern Cooperative Oncology Group from the United States. There is another scale called the Karnofsky performance scale. ECOG is simple in that it goes from zero to four. Zero means that you may have cancer but you are functioning completely normally. You are out at work and you are totally independent. ECOG1 means that you are probably working a little bit but you may have some symptoms from the malignancy. ECOG2 means that you are probably spending a little bit of the day in bed resting and certainly not working. You may need some assistance with activities of daily living. ECOG3 means that you are spending more than 50 per cent of the day in bed. You may have some independence—for toileting and so on—but you need a lot of assistance. ECOG4 means that you are bed-ridden. That is a very simplistic way of looking at it, but it gives clinicians an idea about how functionally impaired the patient is by their malignancy. It will have an impact on what you can offer them in terms of therapies.

Selection of patients is important too. This has an impact on our chemotherapy prescribing. If a patient presents with a potentially curable malignancy your approach to them may be quite different from your approach to a patient who is not curable and who has quite extensive disease—patients with lymphomas, leukaemia, and advanced testicular cancer, in particular. These are potentially curable malignancies and appropriate full dosing, if at all possible, is very important. The next group in the selection of patients refers to adjuvant chemotherapy. This applies particularly to women with breast and ovarian cancer but also people with colorectal malignancy. They have their surgical procedures and there may be evidence that there may be some early tendency for the disease to spread but it is not obvious. The assumption is—past experience has shown—that many of them will have microscopic metastases.

You back up the surgery with chemotherapy to mop up those microscopic cells that have escaped. We have certainly improved outcomes—particularly in things like breast cancer, increasingly in ovarian cancer and, now, in colorectal malignancy. I guess, in time, we will improve outcomes in other malignancies. It is important in that group of patients that the dosing is maintained as close as possible to the optimal dose for them. Then there is another group of patients where cure is unlikely, so we are looking at palliation. I do not mean palliation in the sense of end-of-life care. I mean palliation in the sense of improving the quality of life.

**The Hon. TREVOR KHAN:** What cancers would fall into this third group?

**Dr BELL:** The third group would probably be most of the cancers we tend to think about: patients that are dealing with an active malignancy, maybe liver, bone—

**The Hon. TREVOR KHAN:** Pancreatic?

**Dr BELL:** Pancreatic. It is a malignancy that is incurable or has returned after a potentially curative procedure. You have to say, "We do not have anything that will eradicate this, despite what we may sometimes

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read in the media, but we are going to try and improve your quality of life." One of the best ways to improve quality of life if you have severe pain is to deal with the underlying problem. You do not have to slow the patient up with morphine. Painkillers are important, but to get the patients over the hump and really improve the quality of their lives, if you can control the malignancy with chemotherapy their quality of life may zoom up. The caveat there, of course, is that you do not want to give them increased toxicity from the chemotherapy simply in order to say, "Look, your disease has shrunk by 50 per cent." They will say, "Yes, but I feel wretched." It is there to make them feel better.

**Mr JEREMY BUCKINGHAM:** When you say "optimal chemotherapy treatment", do you really mean as much as they can probably take?

**Dr BELL:** No, that would be incorrect. By "optimal" I mean optimising the dose that their system will be able to tolerate, the maximum tolerable dose for them without causing unbearable toxicity.

**Mr JEREMY BUCKINGHAM:** Yes. The higher the dose—

**Dr BELL:** No, I think there is a bit of—

**Mr JEREMY BUCKINGHAM:** —while measuring the toxicity would be more likely to give a better outcome.

**Dr BELL:** Not necessarily. The concept that you are coming from at the moment I call the North American or US concept that more must be better. If memory serves me correctly, at the end of the twentieth century or in the early twenty-first century there was a vogue in the United States—it was followed here—to give very high doses of chemotherapy to women with breast cancer based on some data out of South Africa by Dr Bezwoda, who has visited this country. I think many of the health insurance companies in the US were forced to support this particular approach. We were using it here, too, until we realised—the Americans did too—that these women were dying faster than women who were treated with standard therapy. What were they dying of? Leukaemias.

We then found out that the data from Dr Bezwoda in South Africa was completely fabricated and fraudulent. So the peer review journals are now taking a much tighter look at data coming through. So more is not necessarily better. There is also a movement—over the last five, six or seven years—for what we call "metronomic chemotherapy", which is a fixed, low daily dose. Patients who have been heavily pre-treated often tolerate that extremely well and can have an improvement in the quality of their lives.

**The Hon. TREVOR KHAN:** What does "heavily pre-treated" mean?

**Dr BELL:** "Heavily pre-treated" may mean they have been through several lines of chemotherapy and their bone marrow is starting to suffer because of that. How do we control the disease to improve their quality of life? We do not give them heavy-duty chemotherapy; they simply will not tolerate it, they will have significant toxicity. So there is a concept of low-dose, continuous treatment. They tolerate that well, and we have found excellent improvements in both disease control and quality of life.

**The Hon. TREVOR KHAN:** Just going back to the "more is not necessarily better", you referred to women having had breast cancer and then having, was it, lymphomas or leukaemia?

**Dr BELL:** The curative treatments at the top: I have got lymphomas, leukaemia, testicular cancer.

**The Hon. TREVOR KHAN:** Do I take it that there was some link between the leukaemia that the women were suffering and the high dosage that they had been receiving?

**Dr BELL:** There is almost certainly a chemotherapy-induced malignancy. So the high dose that we were using—with bone marrow transplantation, I may add, it was suggested the studies out of South Africa were, as I say, fraudulent and led us to, I think, over-treat women—some women.

**The Hon. TREVOR KHAN:** Is that somewhat similar to what happened with men who suffered from AIDS in the 1980s and 1990s where the treatments that they were receiving were leading, by the suppression of their immune system, to a whole series of other diseases? Is that a sort of similar outcome?

**Dr BELL:** I am not an expert in HIV-AIDS, but certainly, I suppose, if you are using any treatment, particularly in the cancer sphere where we are using drugs that themselves are potentially carcinogenic, you have to be having an eye on the future. There are longitudinal studies being done, particularly in the paediatric group, of kids that are now living to their fifties and sixties, through the reproductive age, in terms of what second links we may be inducing.

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**The Hon. TREVOR KHAN:** Is this carcinogenic factor the result of the suppression of the immune system? Is that what the link is?

**Dr BELL:** The link is probably because it is damaging the DNA of some of the stem cells, yes. The last group of patients that do not receive any chemotherapy—and these are the patients where clearly they are too unwell to receive anything more than just systematic control—how do we get to, if you like, best practice in terms of protocols? There are various levels of evidence that are used. If it is level 1 evidence, that means that there is at least one randomised control trial to attest to the superiority of that particular treatment. Level 2 evidence, divided into A or B or 1 or 2, there is at least one well-designed cohort study or case control study. So it is a controlled trial, but not randomised, and level of evidence 2D or 2-2 is comparison between times and places with or without intervention. Level 3 evidence would be just opinions of respected people based on their clinical experience, descriptive studies or reports of expert committees.

Level 1 has kind of become the gold standard, if you like. I have some data to show you that may not always lead to the best outcome. We use in New South Wales eviQ, which is the Cancer Institute of NSW's website, which lists all the protocols that are accepted, and these are constantly monitored, updated; some are superseded, put into the discard basket, and new ones are added. I just wanted to show you metastatic breast cancer—this is breast cancer that has spread. If you look up eviQ you will see metastatic breast cancer and quite a large number of different protocols that people can select from. There is no guidance as to which one is the best. You are using some of the biological parameters about the tumour to make a decision—the patient's general wellbeing in the sense of how healthy they are to tolerate the treatments—but, at the end of the day, it then becomes a discussion between the patient and the treating physician as to what is the one that is most likely to give them the benefit they are after.

I have just pulled out Doxorubicin, which is one of our old breast cancer drugs, and this is directly from eviQ—I just did a cut and paste for the purposes of this morning. You can see it was approved in April 2008, modified just this month, and there will be another review in 2019. The treatment schedule's summary suggests 60 milligrams per metre squared, but what I have highlighted in blue is that the dose can vary from 60 to 75 milligrams per metre squared. The consensus of the reference committee who were suggesting this protocol was that the lower dose is more appropriate for this patient population, unless they are extremely fit or being treated as a first-line treatment for metastatic disease, in which case they are more likely to have a bone marrow transplant that will tolerate the higher dose. But you can see even in our eviQ protocol we are giving a range of advice at one end but not preventing people going to the higher end if they want to.

**The Hon. TREVOR KHAN:** That is a 20 per cent variation.

**Dr BELL:** Exactly. One of the things we are finding out—and I probably should have pointed this out in terms of patient variability—is there is not just a variability between individual patients in terms of who they are but there are racial variations. We find that particularly women from an Asian background receiving certain chemotherapeutic drugs, they metabolise it quite differently from women of a Caucasian background. If we give the women of Asian background the same dosing as a Caucasian-background woman it will cause very, very significant toxicity.

**The Hon. TREVOR KHAN:** And this is to do with liver function issues, is it?

**Dr BELL:** It would probably be more genetic in terms of how they metabolise the drugs. We know, for instance, Asian people in general metabolise alcohol very differently from Caucasians.

**The Hon. NATASHA MACLAREN-JONES:** Is that reflected in this information at all? A doctor looking at it, unless they are aware of other clinicians' views, they would not know to consider ethnicity when it comes to dosage?

**Dr BELL:** They would not because it is not included in eviQ. But if you are doing your job thoroughly I think you would understand with your patient population base that different racial background groups are going to need different treatments, and, given our multicultural society, that has to be considered, particularly in most parts of Sydney these days.

**The Hon. COURTNEY HOUSSOS:** Can I just go back a step? You have shown us several different slides of treatments that were available. You would expect that a doctor would, through their own personal work, have a preference for a couple of those or one of those. What would be normal?

**Dr BELL:** What would be normal is you probably have a preference to two or three different protocols as the first line and you get expert at utilising that—you are experienced with both the delivery of it and the anticipated side-effects and, in particular, the nursing staff that are administering it are going to be doing

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a consistent job and not chopping and changing. But, as I say, there are more than two ways to skin a cat. The unit down the road may use a completely different first-line protocol but it has equal efficacy.

**The Hon. COURTNEY HOUSSOS:** But you would expect that there would be at least more than one option, given the number that are available on eviQ, that there would be more than one option provided to a respective patient?

**Dr BELL:** Absolutely, yes.

**The Hon. COURTNEY HOUSSOS:** And even if they said, "We recommend this one", it would be for a particular reason?

**Dr BELL:** And the recommendation would be based on a discussion with them saying, "Well look, you are in a situation with impaired liver function, you are on a number of other drugs. I think it would be probably appropriate to start with a simpler program, less toxic, and if you tolerate that we have got the capacity to move to something stronger". But one thing we do not want to do is to cause a system collapse with the first treatment.

**The Hon. TREVOR KHAN:** We mentioned earlier "informed consent". I hear what you have just described and I accept it, but—this is unrelated—I am going in for a double hip replacement at the end of the month and my specialist says, "Look, this is what we can do". I say, "Fine, doc. You're the expert. Away you go". I have consented; it is as informed consent as I am ever going to give. Is that what you would describe as "informed consent"?

**Dr BELL:** With chemotherapy you will sign an informed consent form. It should be indicating that it has been thoroughly discussed with you in terms of particularly anticipated complications of a surgical procedure or complications in terms of toxicity of, say, chemotherapy. So the patients are not going in there thinking, "This will be a walk in the park"; most of them do not anyway when it comes to chemotherapy. My job sometimes is convincing them it might be worth giving it a go, to be quite frank. Hip replacement is a little different.

**The Hon. TREVOR KHAN:** I am just interested in the interaction that you have: "This is what we think you should do". You are an empathetic person obviously concerned about your patient and that the patient picks up. You are empathetic, you appear competent. I am just wondering how informed, in a sense, the consent is in that context. You are sitting there—what other choice is there?

**The CHAIR:** The capacity of an individual to process the information would vary from person to person?

**Dr BELL:** Very much so. You will get some patients coming in and it will take you 1½ hours to go through everything because they will come in with a pile of internet publications and their consent is, I would not call it informed, I think it sometimes can be misinformed because they get so confused; and other patients say, "Whatever you think". I find both ends of that spectrum very difficult because I like to engage with the patient and say, "This is your situation. These are the options that we can look at." It has got to be a two-way street. "It is your body, it's your life. You're the one suffering the problem. These are the agents I have but they can be very toxic." And we need to evaluate what they are prepared to put up with. Some women will say, "I'll have any chemotherapy you've got so long as I don't lose my hair". They immediately have consented to something but not consent to any drug that I have got that might cause hair loss.

**The Hon. BRONNIE TAYLOR:** You also say there is a process of consent. The patient sees you, you have a chat and it is fairly overwhelming at that stage and they might absorb maybe 30 or 40 per cent of what you have said. It is probably another week before they turn up at the clinic where they go through a consent process as well with the staff at the clinic. There are different check points if the process is followed, as there should be.

**Dr BELL:** Absolutely. I will often say to a patient at the end of a consultation, "You're not to decide now. You've got to be on the same page as I seem to be on at the moment before you can give that consent. We don't have to decide today. Go away, think about it." And, as you say, they often will come back a week later. They will generally then go through an education session with our nursing staff, sign the informed consent, ask any further questions before they do that and then another day is set for the chemotherapy. So there is a bit of a process in terms of time where they can get through the information and be confident and comfortable that they are making the right decision. I am very uncomfortable with patients who say, "Let's go for it. I want it now." There is an urgency but it is not that urgent that they cannot think about it.

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**Mr JEREMY BUCKINGHAM:** Dr Bell, when you discuss with a patient, is it best practice to put to them a range of options? Do you say, "These are your options; these are the different chemotherapies you could have, the different protocols", or do you just present a recommendation, "This is the drug I believe that you should have at this dosage"?

**Dr BELL:** It is a very good question. Both. You would present to the patient, "We have a range of options." It was simpler 20 years ago when I was practising this because we did not have the range—"If you want chemo this is all you can get". Now there is a range of options and you have to put to them that range—well, I believe you do. Then you discuss with them why your opinion is that this one would be the best. It is usually based on factors that you have picked up in their blood tests, what you have seen on the scans, what you know of their comorbidities and so on. Because all the patients will say—not a lot but many of them—"Just give me the strongest you've got, doc". But you know that if you did that you would make them fall over. You have got to go gently, gently. Even patients that can be very well physically, despite their malignancy, you can give them what is generally an innocuous drug and their own metabolism is not such that it will tolerate it. They can end up in very, very serious conditions in terms of toxicity. So it is a bit of a judgement, that first one. After that first treatment you have learnt a lot more about that patient as an individual and can, I think, give in a sense almost better advice because you know how they tolerate it.

**The CHAIR:** You have led with a very important point. We have all these treatments but you do not know how each individual will respond until it is in their system. I think that is a powerful statement.

**Mr JEREMY BUCKINGHAM:** You said that 20 or 30 years ago there was not an armoury of choices and clearly not as much information, drug options or clinical evidence. Do you think that in the area of oncology people may have been prone to develop a bias towards one particular option; that, through their expertise, they have developed a view that one thing works really well and, therefore, they are prone to recommend that than go through the process of saying, "These are all your options; let's work through them?" Do you think that that culture could develop or is real?

**Dr BELL:** I think that that culture is real. But for any sub-specialty and anything we do in life—if you take your car to a mechanic you rely on the mechanic's advice as to what might be the best way to fix the problem. If you go to your oncologist, there may be a range of options. You will not necessarily go into detail with the patient about what the clinical trials say, what the debates are in the international conferences, but you will say, "These are the ones that can be used, so we have got some options." To me, that is the important thing the patients need to hear. If we try one and that might be my preference for them based on their clinical presentation, I always emphasise to them if there are options, "If that does not work we have got plan B, plan C, plan D". And that is what patients want to hear. They do not want to hear that if this does not work or they cannot tolerate it that is the end. I think this is where I said right at the beginning, we are not dealing just with the physical but there are the emotional, psychological and spiritual dimensions to each patient that we have to bear in mind as we are managing them. And that is the juggling act we have. Chemotherapy is simply one string to our bow as oncologists. The second string is very much the counselling, psychological, spiritual, emotional support we are giving the patient and their carers.

**The Hon. TREVOR KHAN:** In terms of all these different therapies, this was last modified or it was approved on 21 April 2008. Is there much difference in the dosage rates used in 2008 compared to 2016?

**Dr BELL:** No. It is a good question. The same doses have been used over a long period of time. Doxorubicin is actually quite an old drug in breast cancer treatment, and used in other malignancies as well. That dose range has been around consistently. This is not something new. When it was last modified, that was just a review saying, "Yes, this is still an effective drug to consider and will be reviewed again in a few years' time." Local experience, in a sense, is the most important thing. Mr Chair reminded me to talk about some international experience but I thought I probably should touch on our local experience. This is the paper I have for you to take and read at a later stage. I have 10 copies there. I do not think it is terribly complex if you are a non-scientist to get the gist of it.

The Sydney Cancer Centre published in 2009, and that is the Royal Prince Alfred Hospital and Concord Hospital—I have no affiliation with either, by the way. I was at Royal North Shore and I am now at the Northern Cancer Institute. It looked at patients who presented to the Sydney Cancer Centre over a 14-month period. They had 199 patients with non-small cell lung cancer. There were three particular trials that had been published around about that time. The SWOG9509, the TAX326 and the E1594, which is an Eastern Cooperative Oncology Group (ECOG) study. I can give you the drugs if you want to. All of these protocols from these trials are still in eviQ.

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**The CHAIR:** Are you aware that Cisplatin or Carboplatin was used?

**Dr BELL:** Okay. For instance in the ECOG study, that was comparing four different platin doublets. So it might be Cisplatin, there would also be Carboplatin and the doublet was adding a drug like Navelbine—

**The CHAIR:** Cycloplatin.

**Dr BELL:** Cycloplatin you might be thinking of, that is Cyclophosphamide. There are only three platin drugs now too because there is Oxaliplatin we use in bowel cancer. But this was particularly looking at would our patients be eligible to go on to those trials. This, if you like, is the real-world experience, not the rarefied experience of a clean clinical trial to prove a point about the efficacy of a protocol, which may be driven by the pharmaceutical company, may be investigator driven. Only 35 per cent of the patients at the Sydney Cancer Centre presented with the criteria for the E1594. Only 28 per cent met eligibility for the other two trials. The reasons for the ineligibility included significant comorbidities, poor performance data, systematic brain metastases, to name a few things. So only one out of three patients could be treated according to the published protocol. These protocols still exist in eviQ.

If you are utilising eviQ, which we do—with electronic medical prescribing now, the protocol is loaded, bang, into the patient file—you have to go down and look at the data that has led to the decision to put that into eviQ and read the primary documents to see whether your patient will fit and match. Quite often in these trials they are looking for, if you like, very clean patients to prove a point about the efficacy. These patients tend to be younger, on average. They rarely have any significant comorbidities. They tend to have fairly limited metastatic disease, so their prognosis, even without treatment, is likely to be longer than perhaps the average patient we see. They are important studies to do because they do prove efficacy, but the toxicity may be very different because of the type of patient selected from, if you like, the real-world patient.

**The Hon. TREVOR KHAN:** Because I am a lawyer with no medical experience, does that mean that you could not treat essentially two-thirds plus, or seven out of 10 patients, with the right dosage?

**Dr BELL:** You would be treating them, if you like—using the terminology that has become of vogue—off-protocol or modified dosing.

**The Hon. TREVOR KHAN:** Does that mean a lower dosage?

**Dr BELL:** Modified dosing would generally mean you lower the dosage because you are concerned about the comorbidities, their frailty. You may then increase it if you find that they do tolerate it.

**The Hon. WALT SECORD:** Dr Bell, if you are going to diverge from the protocol, you would tell the patient, would you not?

**Dr BELL:** We would normally explain to the patient, "We could not treat you according to the protocol because we would wipe out your bone marrow."

**The Hon. WALT SECORD:** You would tell them that you are doing that: "We are not following the protocol; we are going to do this"—that is, more or less—"for the following reasons"?

**Dr BELL:** I suspect in the current climate there are more and more of us saying that. I would say that in 2009 that probably was not indicated to the patient. These are the protocols, dose modifications would be made. That is done by your general practitioner every time you get an antibiotic—you may get half the dose of the next person.

**The Hon. TREVOR KHAN:** I think we are getting to the nub of this, and I understand why.

**The CHAIR:** Yes, that is why he is here.

**The Hon. TREVOR KHAN:** Would you actually say to a patient, "The protocol dosage is 60 milligrams per metre square. I am going to give you 45 because I think it is going to kill you if I give you 60"? Is that the sort of discussion you would have?

**Dr BELL:** It is the sort of discussion I have, and quite regularly. I treat a lot of women with breast cancer, and they may have been through several lines of chemotherapy. They may say, "I have been in my support group and so-and-so had this drug. Can I have it?" I will say to them, "Certainly you can have it, but your ability to tolerate it at the dose that your friend in the support group had it at is probably reduced because of the previous lines of chemotherapy." We have to walk very carefully.

**The Hon. TREVOR KHAN:** Doctor, I understand that and I accept that, but that is not what I asked you. Do you say, "The protocol is X but I will give you half of that"?

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**Dr BELL:** That is what I am getting to. I will explain to them that we cannot start at what we might regard as the optimal dose because we will cause significant toxicity. So we will start gently, and we can crank it up. I will often indicate to a patient too—particularly in the adjuvant setting when we will often go for maximum dose that is on the protocol, because we are going for a long-term cure or disease control—that we might have to crank it back.

**The CHAIR:** Dr Bell, it would be helpful if we understand the therapeutic index, as it is known. Maybe if you can explain briefly the therapeutic index and that is why a patient may be dosed up and then ride it with a lesser dose.

**Dr BELL:** The therapeutic index is the fact that we are using drugs that kill human cells.

**The CHAIR:** Especially quick cells—

**Dr BELL:** Rapidly dividing.

**The CHAIR:** —such as your hair, nails, and gut lining and that is why you get diarrhoea.

**Dr BELL:** And bone marrow. So the dose that those normal cells will tolerate and the dose at which you can treat a cancer to kill the cancer, the window is very narrow. So I guess that is where the skill of the oncologist comes in, trying to judge correctly the right dose to start with. It may mean to begin with that your first dose is actually below the therapeutic window because you are concerned about toxicity, not necessarily in first line. We are talking about women who may be living 14, 15 years on multiple programs of chemotherapy. They are not getting younger. They are getting older and we have been poisoning them continually for 15 years. You have to be very, very cautious about recommending protocol dosing to them, because that is what you give in first line. In fact, that previous slide with doxorubicin made the point, in blue, "unless fit or being treated in the first line". That was the caveat between the 60 milligrams and 75 milligrams per metre square. They are building into that some advice. If you like, I read between the lines; you have to think carefully about what you are advising here.

**The Hon. BRONNIE TAYLOR:** Sometimes those conversations are precipitated by a side effect, such as methyl xeloda with your hands and your feet. If you come to see your doctor and your hands are peeling and you are on the therapeutic dose, the obvious thing is that there has to be a dose—

**Dr BELL:** —reduction. Absolutely.

**The Hon. BRONNIE TAYLOR:** That is right. That conversation is precipitated by that, or the fact that you have had sepsis and you have ended up in hospital after your first cycle which was within the therapeutic window so you cannot do it again.

**Dr BELL:** Exactly.

**The Hon. BRONNIE TAYLOR:** Sometimes those conversations are precipitated by that, are they not?

**Dr BELL:** Quite often. The initial decision for a dose modification may be based on patient factors that you have already identified, but then ones you cannot identify, like individual tolerability—and the capecitabine xeloda, as you mentioned, is a perfect example. Some of us, and possibly some in this room, will metabolise that very differently and end up with exclusively severe side effects. They may look, for all intents and purposes, to be physically fit and able to tolerate it, and you end up giving them one tablet a day, which is well below protocol prescribing but it works. We tailor treatment to the individual. This is an important concept.

This is not recipe book medicine. It is not a matter of breast cancer—a cup of flour, a teaspoon of sugar, throw in some lemon flavouring and make the cake. This is a guideline as to what would be an appropriate dose for a fit patient who fits the criteria for the trial entry that led to that protocol being on eviQ in the first place. So there are a lot of judgement calls that have to be made. Sadly, sometimes those calls are made after the patient has experienced the toxicity. Fortunately that does not happen all the time. Most of us, particularly if we have been in the business for a while, start to learn how we can modify the doses and we explain that to the patient. They need to know. It is their life, it is their body and they are receiving these toxic substances.

**The Hon. NATASHA MACLAREN-JONES:** How is it reported that you have a majority of people who cannot tolerate the dosage amount therefore they may be given a lesser amount?

**Dr BELL:** It is reported in the notes that we are reducing the dose.

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**The Hon. NATASHA MACLAREN-JONES:** But going back to the pharmaceutical companies or others and to be able to say, "We have a potential problem that people cannot tolerate 60 milligrams."

**Dr BELL:** If it was an unreported adverse event, we would have to report that to ADEC and to the company.

**Mr JEREMY BUCKINGHAM:** What is ADEC?

**Dr BELL:** Australian Drug Evaluation Committee. That would be an adverse event that was not regarded as part of the normal side-effect profile of the drug.

**The Hon. NATASHA MACLAREN-JONES:** In this case, most of them would be normal side effects or a judgement call because you know that they could not tolerate the higher dose?

**Dr BELL:** Exactly.

**The Hon. NATASHA MACLAREN-JONES:** What I am getting to, if it is not reported that the majority of people need to have the lower amount, then how do they know to adjust the dosage?

**Dr BELL:** I think for most of them the trials, once they get to phase 3 and even beyond that to what we call phase 4 trials where many thousands of people have been treated by the drug that the side-effect profile is very well known and established and you know the range in which you can normally move. Sometimes you have to move out of that down, sometimes you can move up and, surprisingly, people's metabolism is intrinsically better in terms of handling drugs. We are constantly tailoring the dose to the individual, but based on the data that has come out of a cohort of patients treated in clinical trials.

**The CHAIR:** So why would you flat dose if you are trying to tailor all these different people in different situations?

**Dr BELL:** As I said, many of the newer targeted drugs are flat dose drugs. A lot of them are a newer agent—what we call tyrosine kinase inhibitors—that is used in a particular type of non-small cell lung cancer. There are three doses for that: 75 milligrams, 100 milligrams and 150 milligrams, and not per metre squared and not per kilogram. The recommended dose is 150. You only drop down if there is toxicity.

**The CHAIR:** Yes, but let us go to the platins. Given all the tailoring that you are talking about and all the micro stuff that you work with, why would you flat dose with cisplatin or carboplatin at 100 milligrams? What would be a scenario in which you would ignore all those other tailoring comments to do that?

**Dr BELL:** I have been talking to date about using chemotherapy to treat the cancer. The other role of chemotherapy and the platins and the anti-metabolites, such as 5-fluorouracil or capecitabine—perhaps I should have mentioned this earlier—can be used for what we call radiation sensitisers. They are not there to kill cancer cells. They are there to enhance the effect of the radiation on the cancer, so we use that in certain circumstances. Head and neck cancer—I am not an expert in that area. I do not treat that. Anal cancer is another area where we are using a combination, but the chemotherapy dosing is usually lower and usually given more regularly because it is not being used for so much its cytotoxic effect but for its radiation-sensitising effect.

**The CHAIR:** So, potentiation?

**Dr BELL:** Potentiation. So you get, if you like, more bang for your buck.

**The Hon. TREVOR KHAN:** My question is not on that point, but you have talked about this tailoring or whatever else. Can you just walk me through this? You have a patient who comes in. We will talk in terms of a woman who has come in for breast cancer. You go through and you say, "This is what we should do." She leaves your rooms. Where did she go to get the dose? I gather it is not given in your rooms.

**Dr BELL:** Yes, it is.

**The Hon. TREVOR KHAN:** It is, is it?

**Dr BELL:** Where you have a day hospital, so you can consult and have a treatment area in the same place. She would not go out of the room and straight in to get the dose. She would go home to consider and I would normally say, "Get back to us with what you'd like to do, questions, and so on." The telephone is an easy tool these days. Then they have an education session with our nurse or the nurse educator the following week before they get involved with it. So there is time for them to consider and ensure that all their questions are answered. I stress that to them: "There is no point having this unless you understand fully what you're getting into."

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**The Hon. TREVOR KHAN:** I was not being in any way critical.

**Dr BELL:** No.

**The Hon. TREVOR KHAN:** I was just wondering because I had assumed that you were not just going to bowl them straight in next door.

**Dr BELL:** Generally, the population thinks that chemotherapy is nasty stuff, and I think they are right. It is very nasty stuff. It is not taking an aspirin for a headache. These are highly toxic drugs. I think a patient needs to be well on the page before they undertake the treatment.

**The Hon. TREVOR KHAN:** When they have decided that this is what they are going to do—they have spoken to their partner or whatever else or their family—they get back in contact. They come back into your rooms, and who gives them the dosage?

**Dr BELL:** If they have decided to go ahead with it, I will prescribe the dosage. We use an electronic medical record that links directly with eviQ. The protocol is downloaded that we have discussed. Doses are calculated automatically in accordance with height and weight, and so on. If there is a dose adjustment, I have to deliberately go into the computer and put a dose adjustment, and there is a drop-down box for the reason I made that dose adjustment.

**The Hon. TREVOR KHAN:** And that is being given to a person over a period of time—I think every 21 days, is it not?

**Dr BELL:** It varies. Some chemotherapy protocols are weekly; some are fortnightly; some are every three weeks. Three weeks is a fairly common timetable for combination chemotherapy agents.

**The Hon. TREVOR KHAN:** Do you assess the patient every time, either before or after they receive that treatment?

**Dr BELL:** No.

**The Hon. TREVOR KHAN:** Or do you organise to see them in three months or so?

**Dr BELL:** No, no, no. The most important time to review them is after the first treatment because that is going to tell you how they as an individual will cope with that treatment. There may be some dose modifications required at that time because of the blood counts and other side effects and so on. That, to me, is the most important visit in terms of how they are going to cope with the treatment. Subsequent visits are more to assess the efficacy.

**The Hon. WALT SECORD:** Dr Bell, you said that a drop-down box comes down and says that a person is deviating from the recommended dose. This is all electronically recorded. Do red flags come up to someone who is supervising a doctor and saying, "This person is continuously"—

**The Hon. TREVOR KHAN:** Yes, that is where I was going.

**The Hon. WALT SECORD:** We are singing from the same sheet.

**The Hon. TREVOR KHAN:** Absolutely.

**Dr BELL:** It is a very good question. We got a brand-new computer program in the last six months, which is driving us all insane, to be quite honest. It is very good but, as you can imagine, with new programs and new software we have to learn. But it does flag that they are on a lower dose. They get a green triangle with a yellow arrow showing that the dose is low. That flags to the nurse and the pharmacist that it has been lowered. We will have the capacity over time to extract all that data out and analyse it.

**The Hon. WALT SECORD:** Does an alarm bell go off and is someone saying to your immediate supervisor, "David's not following this. We should just go talk to him, counsel him, and find out what is going on. There may be a really good reason."

**Dr BELL:** You put the reason in the drop-down box.

**The Hon. NATASHA MACLAREN-JONES:** And what are those reasons, just so that we know?

**The CHAIR:** Normally, what would be some of those reasons?

**Dr BELL:** If it is a second line of treatment or a second dose, it could be toxicity, patient's decision, physician's decision. The physician-stressed decision is usually based on things that the patient may not have perceived but you have noticed their white cell count has dropped to rock bottom and you are terrified.

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**The Hon. NATASHA MACLAREN-JONES:** For how long has that type of monitoring been going on?

**Dr BELL:** I think people are moving more and more to electronic medical records, so we have electronic medical records in public hospitals. Most private clinics are using them.

**The Hon. TREVOR KHAN:** I am not being cute, but what was the position five years ago?

**Dr BELL:** We used paper records.

**The CHAIR:** This seems to be where there is a bit of a disconnect. We know that specialists at the end of the line are giving a treatment that they believe is in the best interest of the patient, whether or not the patient always agrees with that. When a flag comes up and says "No-go, no-go", at the end of the day can a specialist just continue to override the system? Unless they are in a multidiscipline team, they are never going to be found out that they are going down that track, really, are they, because they can chart it however they want?

**Dr BELL:** They can. With the software that has been written, you have to give a reason for the changes, which I think is very important so that you can analyse your outcomes more efficiently. The multidisciplinary team [MDT] is a slightly misused term in that this is when initial treatment decisions are made. Sometimes you might take a patient back to an MDT because there are some complications you need to discuss with the surgeons, radiation oncologists, or whatever, but they do not get continually monitored. If we did that, none of us would ever have time to see patients.

**Mr JEREMY BUCKINGHAM:** That is actually a really important point because it is in the reports we have had that the role of the MDT in the particular case was criticised. But you are saying that the multidisciplinary team is something that comes together at the beginning of the process and does not really reconvene. You might come together and a medical oncologist says, "Okay, this is what I would recommend prescribing here, this particular chemotherapy." The surgeon says, "This is what I have done", et cetera and so forth. Someone else says, "I am managing another condition"—comorbidity, or whatever it is—but they do not then come back together later on in the process?

**Dr BELL:** They may or may not. It depends on the reason for the MDT in the beginning. If it is, say, a breast cancer MDT, a woman has had surgery and they are discussing whether they need radiation treatment, chemotherapy, hormonal therapy and what should be the track to the future to be offered to them, that is where the MDT comes in. They really then have to go back because you have got a management plan established. Patients with, say, pancreas cancer, they may go to an MDT. They are inoperable so the discussion is, "Can we give them chemotherapy first and then maybe operate later on". So they will have the chemotherapy and then get re-presented to the MDT: "This is what has been achieved. Do you think that this is now an operable situation?" It is both, but generally it is a decision-making process at the beginning, not necessarily revisited, but it may be in certain circumstances.

**Mr JEREMY BUCKINGHAM:** But certainly, for example, with a recurrence of a cancer, the surgeon would say, "What chemotherapy have you been getting?" That would be something that would be on their radar. If someone presented with head or neck cancer, they have had surgery, they have had chemotherapy and it reoccurred, that would be something they would be interested in, would it not?

**Dr BELL:** That sort of patient may well go back to an MDT.

**The CHAIR:** I think what Mr Jeremy Buckingham is trying to get to is that you have made a comment that you would bring it all together and have a comment about this particular patient. It is more than likely the next time you meet you will not be discussing that patient; you are going to be discussing some new patient. I think the question is: What would trigger you bringing that patient up again in a multidisciplinary team? Like everyone else, I am thinking what you have is case management by the MDT but you are saying you really do not—you just bring it up once, discuss everything and unless it is highly significant and out of the box no-one really brings that one back.

**Dr BELL:** It is not case management. It is a treatment decision that is made at the beginning. That is probably the most critical time. That is the time you have the best chance of getting the best result—by making a wise decision. That is where multiple heads can be important. And the patient may come back. If the MDT has said, "This is the treatment you need," if the cancer comes back you may re-present them because it is an unusual circumstance.

**The Hon. COURTNEY HOUSSOS:** So recurrence itself is not an automatic reason for a patient to go back to the MDT?

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**Dr BELL:** It is not an automatic reason. A good example would be, say, the woman with breast cancer who has early breast cancer and goes through a process of surgery, chemotherapy, radiation treatment and maybe then some hormonal therapy. Ten years later they recur with multiple secondaries in liver and bone. They do not have to go back to an MDT.

**The Hon. BRONNIE TAYLOR:** When a patient is presented at an MDT, you are looking for, as the name implies, a multidisciplinary approach because we recognised years ago that one modality alone does not work to treat the whole person. If they are going to discuss a bowel cancer or a head and neck, they are going to say, "We are looking at the group of platins." They are not actually going to talk about the dose or the intricacies. Those things get taken on to the next level where the processes come into place, for example, the clinics. You talked about the fact that certain oncologists favour certain protocols because they have had really good results with them. If you were administering that chemotherapy as the nurse, for example, hanging that chemotherapy, if suddenly that dose is different to how that doctor has been prescribing it or how the majority of doctors have been prescribing it, that is when the alarm would go off.

**The Hon. TREVOR KHAN:** Wait a minute. You have asked about seven questions.

**The Hon. BRONNIE TAYLOR:** I do that.

**The Hon. TREVOR KHAN:** I do not know if we have got answers to any of them yet.

**The CHAIR:** I think the Hon. Bronnie Taylor is just running through a process to get to a question.

**The Hon. TREVOR KHAN:** The only thing is that it seemed the doctor was agreeing with some and I do not know if he was agreeing with all that the Hon. Bronnie Taylor was putting.

**The CHAIR:** I think she was running through a process.

**The Hon. TREVOR KHAN:** She may be, but I am learning something and I would like to actually know what I am learning rather than whether the doctor agrees.

**The Hon. BRONNIE TAYLOR:** My question then is: The MDT is not necessarily the appropriate place to pick up whether people are being prescribed on protocol or not, is it? It is more in the process of delivery of the actual drugs.

**Dr BELL:** Yes and no. At the MDT a protocol may be decided in that we may say for breast cancer adjuvant chemotherapy—so having the surgery, chemotherapy after the surgery. They should go on what we call FEC-T—fluorouracil, epirubicin, cyclophosphamide and docetaxel. Everybody knows what that protocol is. We know the toxicity. We know there are going to be certain women where we are going to have to modify doses because of their individual metabolism. But nobody is actually going to write the doses down at the MDT. That point is fair. Nurses hanging up the drugs—that is why we flag why—

**The Hon. TREVOR KHAN:** Sorry, I missed that.

**Dr BELL:** Nurses hanging up the drugs when the patient is actually receiving it—

**The CHAIR:** Intravenous.

**Dr BELL:** —and the pharmacist particularly making sure that the order has gone through will want to know why the dose has been modified from what is in our electronic protocol. That is why we have that drop-down box. If they have some concerns they will certainly always come to us, but generally it is pretty obvious why you have done that and we tend to put it in the electronic record anyway.

**The Hon. TREVOR KHAN:** Five years ago when there was not an electronic record, what would the nurse hanging up the drug have been looking at to work out why this dosage was being—

**Dr BELL:** She would have been looking at what we call a flow sheet. It would have chemotherapy handwritten and signed with generally accepted protocol doses. If you then modified the dose you would write underneath that "reduce drug X by 20 per cent" and it would be clear on the next page of the flow sheet that they had terrible problems with blood count between cycle 1 and cycle 2—it is pretty clear. And I think nurses were experienced at looking at that. Now it is much more refined using the software we have available.

**The Hon. TREVOR KHAN:** What does a nurse do if they feel there is an unexplained reduction in dosage?

**Dr BELL:** I think they would generally speak to the oncologist. In my experience nurses are not very slow in coming forward to ask you why you are doing what you are doing—and pharmacists too.

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**The Hon. TREVOR KHAN:** I had to ask.

**The Hon. WALT SECORD:** I agree with the Hon. Trevor Khan. I am glad he asked.

**The CHAIR:** There has been a culture in medical nursing. As you said, a good doctor will listen to the nurse.

**Dr BELL:** Yes.

**The CHAIR:** Those who have been in nursing also understand that there are a lot of doctors who will not give you two cents for your thoughts.

**Dr BELL:** I will not go into the personality differences that we have.

**The CHAIR:** You do not need to go into that. My point is there is a disengagement of communication and the doctor gets to make the call whether they take that on or not.

**Dr BELL:** They do get to make the call, but they also take the responsibility. I think it should be a much more collegiate approach to the patient. The nurse is there, if you like, as the doctor's agent. But they are very intimately involved with those patients. They are talking to them and delivering the chemo. If you have a good relationship with your nurses, they are going to talk to you.

**The CHAIR:** Absolutely. Dr Bell, we have about 20 minutes left. Is there anything else you would particularly like to draw to our attention?

**The Hon. TREVOR KHAN:** Before we go on, can I say that I was just a traffic court lawyer.

**The Hon. WALT SECORD:** We researched you; you are a bit more than that.

**The Hon. TREVOR KHAN:** I can remember one occasion standing in the foyer of the Supreme Court with a Senior Counsel pointing his finger at me and making very plain that if I ever questioned his decision again he was literally going to kill me. So I understand this concept of collegiality and I also understand the power dynamic of relationships. If a nurse has a doctor—a specialist—who is prickly, where else does he or she go if they feel a patient is being under-dosed?

**Dr BELL:** I would think they would have to go to the head of the department. They would have to go to the person who is actually supervising the whole administration of that department.

**Mr JEREMY BUCKINGHAM:** If you do not want to answer this that is okay. If an under-dosing where nurses and pharmacy were registering their concern or noting it at the very least was occurring, how likely is it that that could occur for weeks, months or years without someone at the management level finding out about that? I do not come from a hospital background. Within the culture of a hospital do you think that that is likely to have occurred? I do not know how many oncologists there are at St Vincent's, for example. Maybe there are a few; I do not know. For instance, do you think it likely that that could have occurred: that for a decade there had been concerns or issues raised about a particular dosing regime and that that would not have registered with other senior clinicians or hospital management? Is that likely in your experience of hospitals?

**Dr BELL:** My experience of nurses is that they are very fast to tell you when they think you are doing the wrong thing. I suppose the culture will be different in different institutions. It will often reflect the personalities involved. You may be a doctor who gets on with everybody, but if the nurses are concerned about what you are doing they will feel quite comfortable in coming to you and questioning you. To me, that is extremely healthy because I think we should all be evaluating what we are doing all the time. I am concerned by the terms "under-dosing" or "off-protocol prescribing".

A lot of our prescribing, as I have tried to indicate, is off-protocol because people will not fit in. Some of the treatments have evolved historically without necessarily good randomised controlled trials to say "that dose is right and that dose is wrong." With some chemotherapy drugs, because of their antiquity, that is the dose you use and nobody is ever going to do a randomised controlled trial to find out if there is a better or more appropriate dose. It is a difficult question. I cannot see a decade-long process where nobody has questioned something that is clearly off-protocol. If it is off-protocol, you have to ask what was the protocol a decade ago. As you can see, eviQ only went back to 2008 for an old drug. That was when it was put on eviQ. EviQ has not been around for a decade.

**The CHAIR:** Cancer care in Australia has greatly improved from the way it was 30 years ago. Now it is way ahead of the game.

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**Dr BELL:** We were in the doldrums during the 1990s, no question about it, while the drug companies were doing a lot of beavering around, developing new products. There was an explosion in the twenty-first century, which is continuing.

**The CHAIR:** And technology.

**Dr BELL:** It is hard enough for doctors to keep up. For patients it is difficult.

**The CHAIR:** Dr Bell, would you like to finish your presentation?

**Dr BELL:** That was the last slide.

**The Hon. TREVOR KHAN:** I am fascinated.

**The CHAIR:** We will continue with questions.

**Mr JEREMY BUCKINGHAM:** While we are doing chemotherapy for dummies, me in particular—

**The Hon. TREVOR KHAN:** You are not alone.

**Mr JEREMY BUCKINGHAM:** What is a clinician? Is a nurse a clinician? Does the term "clinician" capture all those people involved in treatment?

**Dr BELL:** Any allied health professional I would regard as a clinician: dietician, physiotherapist, nurse, doctor. It is a team approach. We perhaps see the doctor as the captain of the ship, but if the ship is going to sail successfully all the team members must play together in harmony. The most important people, who sometimes get left out of that team, are the patient and the relatives. They need to be taken into consideration too. The relatives are looking after the patient and the patient is receiving the chemotherapy. It is all very nice if we, as clinicians, live in harmony, but it is a team effort, with the team including the patient.

**Mr JEREMY BUCKINGHAM:** It seems to me that the modus operandi of all doctors is to do no harm. With these drugs, how important is that? Is your primary approach to err on the side of making a recommendation that could potentially lead to cancer not being treated as strongly as it could be, giving a better health outcome? Would you tend to go in that direction rather than going toward some sort of toxic outcome that could be caused by the medicine you have prescribed?

**Dr BELL:** One of my earlier slides tried to address that, in the sense that there are three broad categories of patient. There are those who are potentially curable by chemotherapy. In that case you might say, "You are fit enough. We can possibly cure this, with a cure rate of 70 per cent. This will be very toxic chemotherapy. You may have a bone marrow transplant. You could go through six months of absolute hell from toxicity. But the outcome is a potential cure." My wife has been in that situation with her leukaemia, so I know what it is like. The outcome has been excellent. It is very personal for me.

The other group of patients are those for whom we think we can improve the long-term outcome by giving them some pretty rugged chemotherapy that is defined by a period of time. That is the adjuvant setting. There might be six months of treatment, then it is all finished and we hope that, with monitoring, we never find it coming back. The third group is where you know you cannot cure them with chemotherapy; you are just trying to make their lives better, with the priority being a better quality of life for as long as possible but not living as long as possible at any cost. Your mindset is quite different there. You may deliberately say, "We want to make you feel better. We do not want to make you feel worse. We might start with a slightly lower dose because of various liver function or renal abnormalities and crank it up if you are tolerating it." The third group are the most unfortunate group that you see. From my point of view, they tend to be the people seeking a second opinion. Everything has failed and they are looking for the miracle cure from me, as if somebody else has somehow got a different recipe book. It is not the case. For them, it is symptomatic care.

**Mr JEREMY BUCKINGHAM:** You said you are not an expert on head and neck cancer, but do you think that head and neck cancers are more likely to be in the third and fourth category? They are more difficult and they are clearly in an area of the body where surgery might not be an option.

**Dr BELL:** When I was a medical student the surgical mutilation that was seen there was absolutely horrific. People would have a cheek removed and half a jaw and have prostheses. It was ghastly. With the advent of better radiation techniques we were seeing cosmetically excellent results with the same cure or long-term survival outcomes. With the advent of using chemotherapy and the drug called Cetuximab as well, which is not chemo strictly, to enhance the effect of radiotherapy you can get an even better result and sometimes with less toxicity.

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Chemotherapy to the head and neck region can cause dry mouth. The salivary glands do not produce much saliva and it can be a very miserable existence afterwards. It is very easy to say, "That is what you should have." One of the lines I often use with a patient who asks my opinion on surgery and radiation is, "I think it is important, but you have to be very certain about it because we cannot put things back or take the radiation out if the side effects are intolerable. With chemotherapy we can get you through that and we modify it or do not go down that path again."

**The CHAIR:** Dr Bell, what is your experience with positron emission tomography [PET] scans? How successful are they? Is it normal procedure to put someone through a PET scan as step one of your assessment?

**Dr BELL:** PET scans are increasingly used and are a very valuable imaging asset. They are not without their limitations, though. They are built up in the media as the be-all and end-all. They are very useful for a patient who presents with, for example, what appears to be a surgically resectable lung cancer. You want to be sure you are not missing some secondary disease that you cannot pick up on an ordinary computed tomography [CT] scan or magnetic resonance imaging [MRI]. It would be horrible to put a patient through lung removal and find six months later that there were secondaries in the liver and you had not done a PET scan. It is there to help decision-making at the beginning. The other use of a PET scan is in diseases like lymphoma, where you can use it to monitor response. It is an exquisitely good way of telling whether the patient is responding. Sometimes a CT scan may not show a change in the size of lymph nodes. They may shrink a little but not completely resolve. Are they reactive nodes now, scarred nodes or is there still active lymphoma? A PET scan can help to determine that. I say "can", not always.

**The CHAIR:** People tend to say, "I have had a PET scan. I am all clear." Then a couple of years later they find out they have secondaries. What is it that the PET scan misses?

**Dr BELL:** It is the limit of detectability. A PET scan will not pick up one cancer cell sitting in your body. That one cancer cell becomes two, four, eight, 16. It seems to be exponential, but it is just doubling over a period of time. It is not so much that the cancer came back. That is the term that we all use.

**The Hon. TREVOR KHAN:** It was always there.

**The CHAIR:** It never left.

**Dr BELL:** It never went away.

**The Hon. COURTNEY HOUSSOS:** I have a question on follow-up care. You said that there is an initial consultation to outline the ideal scenario and to look at some options. The patient would then go away and consult with their family and decide on the course of action. Would they come back to you to confirm that or would that be with the nurses at the clinic?

**Dr BELL:** They would come back to me. We would all have our individual practices in this respect. I would normally say, "This is the information." I will often print out the eviQ protocol for them, because eviQ has a patient print-out sheet, which is really wonderful. You can give them something to go home with. As somebody mentioned earlier, they are not going to remember all the facts from the consultation. They do not; they are completely stunned by the fact that they have cancer and will need chemotherapy.

I like them to go home and read. I say, "Read it. Questions will come up in the car on the way home. Either ring me back, send us an email, and I will call you. We can book you in if you like. So you are pencilled in for next week to start, but we will not start until you are comfortable that you have asked all the questions you want to ask." They then go through the next process of an educating session with our nurses, who give them a lot more reading material and information about the logistics of the clinic. So they feel part of the chemo family—I guess it is not a family you necessarily want to be in—and, if they need to, the patients will come back and see me before the treatment. Or more usually they will say, "I am quite comfortable with all the information." They will then see me after the first cycle so that I can assess the toxicity and tolerability.

**The Hon. COURTNEY HOUSSOS:** To be fair, I think we have established this morning that you have best practice. That is why we are keen to hear what you have to say, because so much of this is a judgement call. You said that you do the initial and then follow-up, perhaps, after the first treatment cycle. What would be the follow-up process after that?

**Dr BELL:** Usually, at the minimum, the follow-up would be every second cycle. For some elderly patients, if you are very anxious about how they will continue to cope, you may follow up every cycle. Ideally, I would like to do it every cycle to make sure that they are continuing to tolerate it, but with the volume of

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patients we are treating that is just impossible. So, unless there is a special reason, after the first one we do it every second cycle.

**The Hon. COURTNEY HOUSSOS:** There would be a set number of cycles and then you would see them every second cycle or every cycle until the end?

**Dr BELL:** Yes.

**The Hon. COURTNEY HOUSSOS:** Then what would be the follow-up or the evaluation after that?

**Dr BELL:** Again, it depends. If it is adjuvant therapy they get, say, a six-month block of treatment, and we hope that the cancer is never going to return. I follow them up—usually in conjunction with the surgeon, radiation oncologist and whoever else has been involved in their care—on a regular basis, sometimes for many years. With my breast cancer patients it is effectively for life. Patients that I treated 20 years ago are now relapsing. If I had not been monitoring them I would never have picked that up as early as I have. I never, in a sense, give them the all clear. I say, "I am very comfortable, but I would like to see you once a year, if I may." For patients who have metastatic disease which is incurable I will be following them until death—generally every six to eight weeks or maybe more frequently, depending on the circumstances and the rate of progression.

**The Hon. COURTNEY HOUSSOS:** How usual would it be that you would say, "I will see you in six to eight weeks," and then they pass away?

**Dr BELL:** In that period of time?

**The Hon. COURTNEY HOUSSOS:** Yes.

**Dr BELL:** That would be most unusual in my practice.

**The Hon. COURTNEY HOUSSOS:** That would be considered one of those unusual outcomes that would require a special conference?

**Dr BELL:** Most units would have mortality/morbidity meetings to look at problems like that that have occurred. They would look at why they have occurred. Was it something we had not picked up in terms of a patient's pre-existing conditions? Was there some error in drug dosing? That is usually not the case. Was it an individual thing? Did the disease progress rapidly through the chemotherapy despite what you were doing? You sometimes see that. Generally, if you have a patient at that end of the spectrum you would not wait two months to see them. You would get them back very quickly. As I said, we normally see them after the first cycle.

**The Hon. BRONNIE TAYLOR:** Could I just ask about the dosing? You are now finding that you can vary the dose, and you put down the reason. Is it fair to say that in the next 10 years—or even over the next two or three years, when the next review is done—that the dosage that is currently seen as the protocol dose could be moved up or down based on the data that is now being put into the system?

**Dr BELL:** My guess is that it is more likely that there will be caveats put around it. As we get more experience with some of the newer drugs we will understand better how to dose manage it. That will be where the protocol is modified. The example I gave was deliberately a very old drug just to show the variability that is still there in a drug that we have been using for decades. The newer drugs are going to be monitored and re-evaluated more frequently. Advice will be given to clinicians prescribing as to adjustments they may need to make. The longer you use a drug the more you understand it—particularly some of the rarer side effects. I have to emphasise that this protocol dosing is a guide to where you can start. You may not start at that point; it is not an absolute recipe.

**The Hon. TREVOR KHAN:** It is a start in the context of your saying, "For a health patient who is 35 years of age with no comorbidities, that is the dosage."

**Dr BELL:** That is what most of them will tolerate well with an acceptable toxicity.

**The Hon. TREVOR KHAN:** So it is a starting point for that purpose but then it simply forms, in a sense, the reference point from which you adjust for all those other factors.

**Dr BELL:** Yes, all those other factors. The other factors that come into the equation are the new drugs and new protocols. That is why eviQ continues to expand. You will find when you log into it that there are superseded protocols—things that we used to use that are no longer regarded as appropriate treatment. That is not to say that they were bad treatments 20 years ago, but we have a lot of new ones.

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**The Hon. TREVOR KHAN:** Am I right in saying that the other factor is—we have all talked about this in the context of chemotherapy treatment—that it is not being used in chemotherapy but it is used for something else; I cannot remember the terminology?

**The CHAIR:** Palliative or potentiate?

**Dr BELL:** The other use of chemotherapy is to potentiate the effect of radiotherapy in, as I mentioned, cancer of the anus, head and neck tumours—

**The Hon. TREVOR KHAN:** For that group, all these protocols with regards to dosage, in that sense, are irrelevant at that point in time. Is that right?

**Dr BELL:** Yes, because these are for using chemo as a strategy to control the cancer. There will be some protocols—well established for anal cancer—in terms of the drug dosage you should use there. I am less familiar with the prescribing protocols for chemo sensitisation in head and neck tumours.

**The Hon. TREVOR KHAN:** But there would be a separate protocol for that?

**Dr BELL:** Yes.

**The CHAIR:** Can you give us a quick understanding of the effects of cytotoxic drugs and non-cytotoxic drugs?

**Dr BELL:** Do you mean in terms of cancer treatment?

**The CHAIR:** Yes. You had it up on the screen.

**Dr BELL:** We are talking a lot about chemotherapy. When I was a medical student chemotherapy was antibiotics. I have a textbook at home to prove it. It has now been taken by oncologists and the public at large to mean the drugs that we use to treat cancer. The general feeling is that they are all nasty. We have broadened that out to talk about some of the hormonal agents that have been around for a long time—like tamoxifen in breast cancer—and some of the anti-angiogenic substances that stop blood vessels growing, like Avastin. There are also some of the antibodies we use in bowel cancer, like Cetuximab, and Herceptin and Trastuzumab in breast cancer. They all come under the umbrella of chemotherapy. I think we really mean cancer drug treatments.

Some of them are not cytotoxic. They work through much more subtle mechanisms. In fact, to me—this is the explanation I give to patients—chemotherapy is a bit like using weedkiller on your lawn. We spray the whole lawn hopefully to kill the weeds. But it is not particularly subtle. The lawn may suffer for a few weeks but hopefully the therapeutic window will allow the lawn to grow and the weeds will die. The drugs that are being developed now are targeted drugs, which, interestingly enough, tend to come with a fixed dosing. They are not without toxicity, either, but they are much more selective in the target that they are hitting. So the side-effect profiles, in general, can be somewhat lower.

**The CHAIR:** I noted that Mr Jeremy Buckingham spoke about clinicians. In the studies I have read in the journal on oncology, they talk about clinicians and academics but they are operating as oncologists. Do you know what the breakdown is? Is an academic someone who is just studying and writing papers, whereas the clinician is focusing on patient outcomes?

**Dr BELL:** In this country we talk about clinical academics. Most of the academics are not just sitting—

**The CHAIR:** They are all one and the same?

**Dr BELL:** They would have an academic appointment at a university. They would be teaching but they would be treating patients. The terminology of "clinician" or "community oncologist"—that is the one they use in the United States—is for somebody who does not do any clinical research. They will be treating according to what their academic colleagues say is the best practice for this disease.

**The Hon. BRONNIE TAYLOR:** Just one last thing. We spoke a lot about doctors and nurses and how often you see a patient. I think it gets lost in that whole thing about all the other primary care interventions in terms of, say, a breast cancer patient who has access to a McGrath nurse who is going to follow her all the way through. So that if she is really sick and I am the nurse I am going to ring you and say, "Dr Bell, she is really bad; we need to do something", and then you will see her or whatever. The point I am getting to, reading through a lot of this stuff and having my own history as a cancer nurse, we have lost sometimes that ability to coordinate that care from go to whoa. We have had attempts at it with care coordinators and things. Do you

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think that is something that we need to revisit to keep more of a connection through this whole spectrum of health professionals that the patient is seeing?

**Dr BELL:** Yes, and I think that is developing. I think the McGrath breast nurses are a great example of it as they have expanded into the community. They will see patients in their home, they will ring me. Community nurses will ring me: "We're seeing Joe Bloggs today and he's not very well"—because I cannot be in the home all the time. But we should not leave the GP out of the equation either because the general practitioner is the person who has probably known them for many years and, hopefully—some of them still do—will do a home visit.

**The Hon. BRONNIE TAYLOR:** That is such a good point, because often the GP, particularly for rural patients, gets left out of the loop once they see the oncologist.

**Dr BELL:** Absolutely, and sometimes that is the patient's fault as much as the GP's fault. The patient does not feel that the GP has the knowledge to deal with the fact that they have not just caught a common cold, it has got to be the cancer. Sometimes the GP feels very uncomfortable personally dealing with a diagnosis of cancer and so they are quite happy for the oncologist to almost take on a GP role. But a good GP will be an integral part of the team and, in fact, I think the cement in the team, because they know the patient very well. Community nurses, yes.

**The Hon. BRONNIE TAYLOR:** We need more of that sort of holistic approach?

**Dr BELL:** Yes.

**The Hon. NATASHA MACLAREN-JONES:** Following on from that, what have been the big differences as you have seen from 10 years ago in this area to now? We are talking about the McGrath nurses and things, they are all more recent activity. What are other variables that you have seen changed?

**Dr BELL:** I think the explosion of multidisciplinary teams where complex patients—

**The Hon. NATASHA MACLAREN-JONES:** They did not exist?

**Dr BELL:** They did not. They existed probably a decade in breast cancer and are growing in other areas too. Allowing us to talk with the pathologist, the radiologist, the radiation oncologist, the surgeon, the medical oncologist—all talking about it. Also now with the breast care nurse in the room, sometimes the patient will come in. We always invite the GP to come—they rarely do because it is time out of their day—to just get that team feeling that we are interested in this particular patient, what is going to deliver the best outcome. So that, to me, has been the biggest change in the last decade and it is continuing to evolve.

I think we do need, to be perfectly frank, to revisit how valuable it is to present every single patient at a multidisciplinary team [MDT], because some of our breast MDTs we can have 20 patients to discuss. There is some work done in Memorial Sloan Kettering in the thoracic unit showing that probably only about a third of their patients really needed to be discussed in an MDT because their clinical pathway was so clear. So you do not have to just tick the box for the sake of ticking the box; it is there for a particular purpose.

**The Hon. NATASHA MACLAREN-JONES:** You did mention a little while ago that you wanted to be reminded about something in these international studies.

**Dr BELL:** In the United States a lot of patients—around about 60 to 70 per cent—are treated, if you like, off-protocol—it is not really off-protocol; it is modification of a protocol due to the circumstances. Protocol treatment is based, as you will see in this article, on trials. That is what goes in, but when you actually evaluate who would be eligible for that trial there is only one in three.

**The Hon. TREVOR KHAN:** Just before we close off, and I am doing this in front of the doctor for a reason, what is our intention with regards to Dr Bell's evidence?

**The CHAIR:** That is a very good question. Dr Bell, would you be adverse to us using your brief publicly?

**Dr BELL:** I was told that it would be.

**The CHAIR:** If you are open to it, we can use your evidence; it will be immensely helpful to us for education purposes. For our inquiry purposes it will be a gift you have contributed that keeps giving. We thank you for your time and your expertise. If someone wants some further independent information, would you be happy to get an email from any of us asking for some clarification?

**Dr BELL:** Absolutely. It is a complex area and I am very happy to try and clarify it.

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**The CHAIR:** If you feel conflicted, by all means just say no.

**(The witness withdrew)**

**(The Committee adjourned at 11.00 a.m.)**