The London experience - The TGN 1412 Trial

Dr Arthur Rallis is a senior researcher from the Corporate and Financial Services Group at the Melbourne office of DLA Phillips Fox. In addition to being a lawyer, he holds a medical degree. His area of expertise includes commercial law, health law and privacy. A large component of Arthur's practice involves providing advice to clients in the health sector, including public and private hospitals, medical practitioners, dentists and pharmacists. He has reviewed and drafted a broad range of agreements for the health sector.

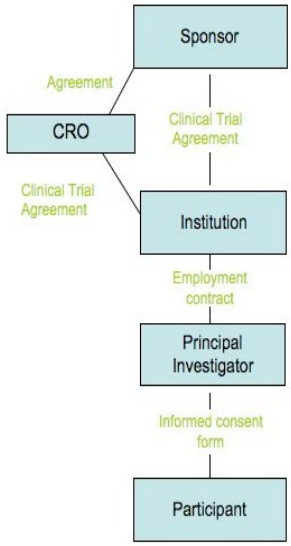
In the area of clinical trials, Arthur regularly advises public and private hospitals in relation to a wide range of relevant legal issues, including consent of participants, liability and indemnity issues and clinical trial agreements. He also advises the insurer of the Victorian Public Health Sector in relation to its clinical trials program.

Why are lawyers involved in clinical trials?

Very often, when I explain to people that I regularly advise in relation to clinical trials and research, people are perplexed. Why do you need lawyers involved in relation to the conduct of clinical trials? For clinical trials, don't you need patients, hospitals, doctors and drugs? That's about it. Where do lawyers fit in? That's a very good question — and there is a very good answer.

Lawyers fit in because, just like everything in this modern world, the conduct of clinical trials often involves a number of complex commercial transactions. I will give you a brief overview of those because it is important to understand these arrangements in the context of what happened with *TeGenero*, *Parexel* and the whole drama with TGN1412.

The matrix of arrangements for the conduct of clinical trials



Commercial arrangements in clinical trials

I have set out a matrix of commercial arrangements regarding the conduct of clinical trials for commercially sponsored studies.

A lot of studies, in Victoria at least, and I am sure in New South Wales as well, are investigator initiated, but given that *TeGenero* was a commercially sponsored study, I will focus on the matrix for commercially sponsored studies.

At the very top sits the commercial sponsor, a drug or pharmaceutical company like *TeGenero* which initiates the study. In order to get a study happening, the drug company needs participants — it needs investigators and facilities to conduct each particular study, and that is where the institution comes in.

In almost all cases, there will be a comprehensive clinical trial agreement governing the relationship between the commercial sponsor and the institution. In the *TeGenero* case, we had the interposition of a contract research organisation (CRO), *Parexel*. A CRO is sometimes used by a commercial sponsor, such as a drug company, which doesn't have a presence in a particular market or in a particular country. It requires the

CRO to conduct and administer the study on its behalf. Obviously, there are arrangements between the drug company and the CRO regarding their respective rights and obligations. The most important of these, from the perspective of the patient in a hospital, are very often the obligations concerning indemnity, liability and insurance, because, if something goes wrong, these are the most relevant issues.

The principal point of contact — the person who really has the day-to-day running of the study — is the principal investigator. Most often, the principal investigator is an employee of a particular institution. At the very bottom of the matrix, but certainly not in any way representing their importance to the whole process, are the participants; they are, of course, crucial.

Adequately informed consent

Professor Cunningham has discussed the informed consent process and whether or not the informed consent in this particular case was adequate. Generally with clinical trials, at the time a participant is approached, say a patient in a hospital, and asked whether or not they would like to participate in a study, there will be some discussion about the study. If they indicate that they would like to be involved, they are provided with a 'participant information sheet and consent form. This is a comprehensive document, running anywhere from five to 25 pages. It describes what the study involves, the participant's involvement in the study, the risks involved and a whole range of other issues, such as access to information collected about them and so on. It is often a detailed document which is, I am sure, difficult for some participants to comprehend in what is sometimes a very brief time before they are actually enrolled into the study.

At the very end of that document is an informed consent form. If the patient is happy to participate in the study, they sign the form.

Agreements and contracts

There is some judicial authority in the United States which indicates that the participant information sheet and consent form, in fact, constitute a contract. Although I am not aware of any case in this country where that principle has been upheld, that notion, for a number of reasons, troubles me a little.

Key organisations involved in TGN 1412 trial

Role	Name	Location
Sponsor	Tegenero AG	Wurzburg, Germany
Manufacturer	Boehringer Ingelheim	Germany
Contract Research Organisation	Parexel (U.S. Company)	United Kingdom
Institution Conducting Research	Northwick Park Hospital	United Kingdom

The relevant parties in the TGN1412 trial

At the top is the sponsor, *TeGenero AG*, a German company. The drug manufacturer was *Boehringer Ingelheim*, based in Germany. The CRO, *Parexel*, was a US company.

Parexel operates all over the world. There are many studies being conducted today in Australia by *Parexel*. The institution conducting research was the Northwick Park Hospital. Something omitted from the first chart was the ethics committee, which I grouped with the institution (the hospital). The ethics committee, which is absolutely crucial to this whole process, is generally attached to the relevant hospital at which the study is being conducted.

The risk of being sued

One of the major concerns of all ethics committees is the likelihood of being sued in the event that something goes wrong. Whenever I speak to researchers and members of ethics committees, that is their number one concern. They are worried that, if they approve a particular study and something goes wrong, they could be liable. There are numerous reasons, which I won't go into, why many of their concerns are unfounded; these revolve around the indemnities provided by their employer — by the hospital to which they are attached — who would ordinarily pick up any liability in the unlikely event that something did go wrong.

I am not aware of any case in Victoria, or indeed in any other state, but particularly in Victoria, where a member of an ethics committee has been sued for something they have done or failed to do in relation to a clinical trial. I am almost certain that ethics committee members would have been sued in the US, but that is the US, where anything that moves is a possible target for a lawsuit.

The legal issues in the London trial

There is always a lot of scuttlebutt surrounding these types of incidents. Although the scuttlebutt is often more interesting than the facts, let's stick to the facts.

Payments to the volunteers

There is no denying that the patients who were recruited, the volunteers, were paid £2,000 to compensate them for their effort, their time, their trouble and so on. There have been some reports that one of the participants was pretty much a professional clinical trial volunteer who had earned up to £50,000 in the previous year through this activity. When you think of the pre-tax amount which that represents, it is a significant sum (probably more than that paid to the researchers conducting the study).

The question of payment is certainly an ethical, and possibly a legal issue as well. There is an argument that an amount of £2,000 represent coercion or an undue influence. Aren't you really enticing people and affecting their decision to participate in a study in circumstances where they wouldn't otherwise volunteer? This might be more relevant for unemployed people or patients of lesser means. Often £2,000 is a significant incentive. It is questionable whether or not it tarnishes the consent.

Adequate disclosure of risk?

Whether or not there was adequate disclosure of all the risks has surfaced in a lot of the literature. There are various reports that all the known risks weren't disclosed. Of course, the question is: Had they been disclosed, would it have made any difference, would these people have signed up in any event?

The participant information and consent form

In just about every one of these forms, under a section typically headed 'Risks and Discomforts Involved in This Study', there is included a paragraph stating, "There may be additional unknown or unforeseen risks in relation to your involvement in this study." This is really a catch-all which says, "Okay, there are a lot of things that we don't know; these could even be life-threatening or even fatal. We are just letting you know that you are exposing yourself to this risk and this is what you are signing up for." Sure, it is fine to say that you inform people that there might be unknown or unforeseen side-effects, but does that get you off the hook if there is a significant adverse event?

Negligence

At law, it won't if you have been negligent. You can say that something unknown, unforeseen or untoward might happen, but if your conduct is negligent and leads to injury, it does not necessarily follow that you can then point to that statement and say, "I told you there might be unknown or unforeseen risks."

Compensation

As a result of their participation, these participants suffered some quite serious and grave physical ailments. Obviously, they would be looking, and some have been looking, for compensation. They have been attempting to identify possible claim targets. When something of this magnitude goes wrong and numerous parties are involved, I guess that a claimant would seek to pursue the party which is believed to be most responsible and which has the greatest capacity to compensate.

In my first chart, I lined up all the parties involved in this study. So the question is: who do you go after, against whom can you make out a case that they had, in any way, been negligent? At one extreme, you could say that each and every one of those parties has, in some way, been negligent.

The likely targets

Let's take it from the top. *TeGenero* is the most likely target to go after. Certainly, the lawyers for a number of the injured patients have targeted *TeGenero*. They are the ones who designed the protocol, they set up the processes, etc. But there are also quite compelling arguments that some of the other parties were responsible and were possibly negligent.

What is the role of the contract research organisation, *Parexel*? It administered and oversaw the study. In effect, it steps into the shoes of the sponsor in relation to the conduct of the study at the hospital. Should *Parexel*, a world-wide CRO with extensive experience, have known better? When it picked up the protocol and read it and had its experts review it, should it not have identified any flaws, if there were flaws?

An argument could be mounted that, as part of the ethical review, the ethics committee might have overlooked certain things which should have been picked up. The same goes for the hospital and the investigators. An argument could be made that they also failed to pick up certain fundamental problems with this study, problems which they should have identified.

Reasonable foreseeability

Lawyers will be aware that, if you suffer an injury as a result of something someone else does, you really have nowhere to go unless you can prove that they have been negligent; a core element in establishing negligence is the concept of 'reasonable foreseeability'. If you can't establish that the injury you suffered was reasonably foreseeable, your claim will fail.

There are many opinions as to whether or not the outcome in this case was reasonably foreseeable. Let me give you two divergent views.

The plaintiff's lawyer's argument

This won't surprise you. This particular lawyer for two of the injured participants actually published her views on the case on her web site, something which lawyers in Australia haven't readily embraced. She says:

"I am surprised that *TeGenero* have chosen to file for insolvency before the compensation claims had been considered, thereby causing further alarm and

psychological distress for our clients… We believe that there are good grounds against both *TeGenero* who manufactured the drug," (well, in fact *Boehringer* manufactured the drug) "and *Parexel* who were responsible for managing the trial. I would also fiercely dispute the statement by *TeGenero* that the adverse reaction of our clients to this drug was unforeseeable. We believe there is increasingly strong scientific evidence which supports our view."

The view of the Medicines and Health Care Products Regulatory Agency

Professor Cunningham has referred to the Agency's differing opinion. The Agency concluded:

"This investigation indicates that the adverse incidents did not involve errors in the manufacture of TGN1412 or its formulation, dilution or administration to trial participants. We therefore conclude that an unpredicted biological reaction of the drug in humans is the most likely cause of the adverse reactions in the trial participants. In this case the resulting activity seen in humans was not predicted from apparently adequate pre-clinical testing."

If a court were to adopt that view, it is not looking very good for the patients.

Compensating injured patients

However, the conduct of clinical trials represents a slightly different ball-game when it comes to compensating injured patients. In this country, when a commercial sponsor conducts a study — in Victoria and New South Wales, and I am fairly confident that it is the same in other states — the commercial sponsor is required to provide indemnity to the hospital in relation to that study. The indemnity states that the sponsor agrees to compensate participants on a no-fault basis, in accordance with some guidelines issued by the organisation *Medicines Australia*.

Medicines Australia, which represents the interests of pharmaceutical and device companies, has set up the 'Medicines Australia Guidelines for Compensation for Injury' for participants injured in clinical trials. What this, in effect, sets up is a no-fault compensation scheme. The hitch is that it is purely voluntary; at any time, a drug company can decide to opt out of the system.

There are obviously compelling reasons why a drug company would not want to opt out: not only would it tarnish its reputation but the reputation of all other drug companies conducting studies but it could make hospitals less likely to take on that company's commercially sponsored studies.

In general, the drug companies approach hospitals and say, "Okay, if something goes wrong, we agree to provide a certain level of compensation to participants — no questions asked." Well, some questions are asked, but generally the patient won't have to prove fault and go through the whole court process of establishing negligence. This is obviously in the best interests of the drug company; they don't do it simply for altruistic reasons. And, of course, there are qualifications within those compensation guidelines as to what payments are made and what level of compensation is payable.

Compensation in the London study

As best as I can determine, some of these participants were compensated on that basis. I say that because I understand that, earlier this year, there were some meetings between *TeGenero's* insurer and the lawyers for some of the patients, whereby they would discuss compensation. The UK has a similar no-fault compensation scheme, developed by the Association of the British Pharmaceutical Industry. *Medicines*

Australia pretty much copied and adapted that particular scheme.

Insurance

Because the commercial sponsors who pay out such compensation have insurance, the compensation payment is not necessarily coming out of their own pocket. They have insurance policies in place which specifically contemplate the possibility that they would have to compensate participants under this scheme. This is an important risk management measure to ensure that, if somebody is injured, they are not left high and dry — the participant will ultimately receive compensation.

The impact of the Duff Report

Professor Cunningham has discussed the Duff Report in detail. I am really not an authority to speak on whether or not there is a need to improve or change Australian protocols and authorisations. What I can say is that, in the last eight to twelve months in Victoria, the VMIA, our statutory insurer for clinical programs in our public hospitals, has put out some 'first time in human studies' guidelines for use by hospitals. Those guidelines and protocols are just starting to be taken up by Victoria's public hospitals.

Risk management

From a legal, risk management point of view, the provision of adequate indemnities by sponsors is crucial to protect the interests of the hospital. I particularly say 'the hospital' because, if a patient can't go after a drug company, they will often go after the hospital. When a commercial sponsor conducts a study in Victoria or New South Wales, not only must they provide an indemnity to the hospital, but also evidence of their insurance arrangements, with certain minimum levels of insurance.

Currently in Victoria and in New South Wales, the cover is $10 million per occurrence and in the annual aggregate. *TeGenero's* policy had a limit of only £2 million. There is a real concern around the solvency of small drug and pharmaceutical companies; that concern is compounded in the light of a very small insurance policy coverage limit.

The fate of *TeGenero*

TeGenero provides a classic example of what can go wrong and why we need to have in place risk management measures whereby we compel the sponsor to provide indemnity and a certain level of insurance. *TeGenero* pretty much went insolvent overnight when this catastrophe happened. Because it is a small start-up company, all it is really doing is burning cash — not yet generating any revenue. It is relying on its intellectual property to get it through, to become profitable at some time in the future. When something catastrophic happens, the organisations which have been putting money in to such company cut off the supply. Overnight, the company becomes insolvent. What assets could it have? A few test tubes and a few computers. It is probably renting its premises. It wouldn't have any assets.

So when a hospital arranges to conduct a study with an organisation like *TeGenero*, which essentially has no assets, and which has an insurance policy with relatively inadequate liability limits, the hospital is running a grave risk that if something goes wrong, it will be subject to an unfunded exposure. The commercial sponsor won't have sufficient money. Is it possible that *TeGenero* could ever trade its way out of trouble and become solvent and accumulate resources? Highly unlikely. Very few companies come back from the brink.

Constraints on claims on an insolvent company

A great impediment when dealing with an insolvent company, or a company where a manager a receiver has been appointed is that there are constraints on the claims you can make against that company. Under the Corporations Act, you need the permission of the receiver or the consent of the court to initiate proceedings against that company. So you are really stuck. You have got nowhere to go. If there is insurance, yes, there are provisions that allow you to go after the insurer directly, but if the company has a policy with only £2 million, you are not going to get very far if there are multiple or large claims that will exceed such limit..

Tighter rules?

So the question that comes up is: Should different rules apply? Should we impose even stricter requirements on small pharmaceutical and device companies which are trying to scratch out a living by trying to develop a new product? I leave that for you to consider. In my view, this would be met with extreme resistance, not only by those companies, but also by the investigators.

Could this have happened here?

This is probably the most important question of all. I have my thoughts on this, but I would be curious to know your thoughts. Could the TGN1412 study have progressed, have been approved, have been initiated — in this country? Sure, *today* we can say, "of course not", but we have the benefit of hindsight. If we could jump into a time machine and go back to January 2006 and if *TeGenero* or *Parexel* approached your institution (for the doctors and researchers in attendance tonight) with this protocol, would your institution have approved it, would it have gone ahead and could we possibly have had these disastrous results here?

The only thing I will say is that in New South Wales and Victoria, the answer to that is probably "No", because of the very low limit on *TeGenero's* insurance policy, but had *TeGenero* or *Parexel* come up with a policy with at least $10 million, I am not sure that the answer would still be "No."

This publication is an edited version of a presentation given to the Medico Legal Society by Dr Arthur Rallis on 14 November 2007. It should not be relied on as a substitute for legal advice. Specialist legal advice should always be sought in relation to any particular circumstances and no liability will be accepted for any losses incurred by those relying on this publication.