PEER REVIEWED | Keymanthri Moodley, MBChB, DPhil

An Investigator's Perspective on Litigation in Clinical Trial Research

A central concept in the debate surrounding research ethics is the important distinction that must be drawn between the doctor-patient relationship in a treatment setting and the investigator-participant relationship in a clinical trial setting. Traditionally, the doctor-patient relationship is centered on care and concern for individual patients. The patient is the focal point for that care and concern, and generally, any decision-making is done in the best interest of that patient. Despite this context of beneficent care for the patient, the presence and possibility of malpractice litigation in clinical medicine are established and firmly entrenched.

On the other hand, in the clinical research context, the investigator-participant relationship differs significantly. In this setting, where specific investigational products are tested on appropriate research participants, the concept of benefit to the individual participant plays a minimal role. Indeed, in any clinical trial, there may be no significant benefit for the participant. In the clinical trial setting, the benefit to science and society is the focal point, and positions the research participant as a means to an end. Furthermore, there is a perception that in a clinical trial, the investigator goals may very well not be aligned with participants' best interests. As a result, the nontherapeutic relationship between trial participant and investigator requires special protection of the participant's rights. When this protection fails to occur, litigation is likely to enter the world of clinical trials.

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In the clinical research setting, litigation differs significantly in many respects from litigation in the patient treatment setting, such as in the naming of defendants, the allegations made, and financial settlements reached, especially where class action is invoked.[1,2] This article provides a non-lawyer's perspective of these basic elements of litigation in clinical trial research.

Unlike medical malpractice litigation, where the defendant usually is the patient's individual healthcare provider, litigation in clinical trials can name almost all members of the research enterprise as defendants. This could include investigators, institutions, sponsors, research ethics committees (RECs) or individual REC members, contract research organizations (CROs), bioethicists, and regulatory agencies. In the case of *Weiss vs Solomon*, a trial participant had a cardiac arrest and died after a fluorescein

angiogram that was part of the study. His family sued the investigator, the hospital, and the referring physician. However, the court found that only the investigator and hospital were liable, not the referring physician. The hospital's liability was based on its REC's approval of a deficient informed consent form.[2]

Also, in the well-known litigation around the participation of 18-year-old Jesse Gelsinger in a gene therapy trial at the University of Pennsylvania,[3] several defendants were named. Gelsinger's family sued the trustees of the university, two hospitals, the investigators, the sponsor, the ex-dean, and the bioethicist involved. Clinical trial litigation can therefore have an impact on any combination of role-players from the research team.

Clinical trial litigation may also involve a broad spectrum of allegations against many defendants. Some allegations may pertain directly to the conduct of the trial; others may involve issues that arise after the trial, such as compensation for research injuries and post-trial provision of treatment. Although most allegations are resolved in national settings, some cases take on an international perspective, as may be seen in the Trovan/Pfizer case discussed later in this article.

Trial-Related Allegations

Informed consent is equally important in human subject research and in patient medical care. However, generally speaking, the standards of and process for informed consent in clinical research are higher than those for informed consent in the course of medical care and treatment. One simple and practical illustration of this degree of difference in informed consents would be the number of pages of a consent form for a surgical procedure in the ordinary course of treatment versus the consent form for a clinical trial of an experimental drug or device. In the doctor-patient treatment relationship, it is essential that the patient be informed of the risks that are material to his/her decision-making around a particular course of treatment. In clinical research, the participant is not looking at a known standard of therapeutic care, but rather at involvement in an experiment in which the unknowns are many. In this research context, all reasonably foreseeable risks are disclosed to the potential participant, together with the probability of each risk occurring. This may very well include the risk of death, irrespective of how small that might be.

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This was illustrated in the Nicole Wan case in 1996. This healthy 19-year-old University of Rochester student was enrolled in a research study requiring bronchoscopy and alveolar cell lavage. She required large doses of the anesthetic Lignocaine, due to the discomfort associated with the bronchoscopy. After the procedure, she complained of chest discomfort, but was discharged home later that day. At home she developed an epileptic fit and was brought back to the hospital, where she died after a cardiac arrest. Her postmortem revealed that she had received 1,200 mg of Lignocaine, instead of the 300 mg specified in the protocol. Furthermore, the consent form did not mention the possibility of death as a risk of the procedure.[4]

The Gelsinger case also illustrates allegations around informed consent deficiencies. Jesse Gelsinger's condition involved a partial deficiency of the ornithine transcarbamylase enzyme. During the clinical trial in which he enrolled, Gelsinger died after a gene infusion carried by an adenovirus vector. An inquiry into his death revealed that, among other deficiencies, adverse events detected in other human trials and in prior animal studies, including death, were not included in the informed consent form.[3]

In a 2001 study of hexamethonium at Johns Hopkins University, several legal deficiencies were found in the study's informed consent process. This drug was previously used to treat hypertension, but was found to be ineffective and was deregistered for that purpose by the U.S. Food and Drug Administration (FDA). The new clinical trial was looking at a possible new use for hexamethonium; the drug was administered by inhalation to healthy volunteers, including Ellen Roche, a 24-year-old employee of the Asthma and Allergy Centre at Johns Hopkins. She died a few days later.

The investigation into Roche's death revealed that the informed consent form was deficient in many respects. Hexamethonium was described as "a medication that has been used during surgery as a part of anesthesia; this is capable of stopping some nerves in your airways from functioning for a short period."[5] The side effects of hexamethonium were not fully listed. The section on risks stated that hexamethonium "may reduce your blood pressure and may make you feel dizzy, especially when you stand up." Pulmonary toxicity, the major cause of Roche's death in this study, was not mentioned. The experimental nature of

the drug was not clarified, but instead it was referred to as "medication."[5]

Conflict of Interest

Failing to disclose a conflict of interest in the research informed consent form is another deficiency and may result in a charge of fraud against investigators.[1] Such an allegation has ethical and moral overtones that make it a highly charged and financially more viable claim in clinical research litigation.

Again, the Gelsinger case is illustrative. In this case, it was prominently alleged in the court papers that the university was to receive an ownership stake in Genovo, the company sponsoring the research. In fact, it was alleged that both the university and the doctors involved in the research had equity and financial interests as to the viral vectors used in the study.[3] For whatever reason, this conflict of interest was not disclosed to Jesse Gelsinger in either the informed consent form or during the informed consent process. An undisclosed conflict of interest implies that the informed consent process is faulty because the potential study participant is not fully or truly informed.

The pivotal role of the informed consent process in clinical trials is underscored by the host of allegations related to its deficiency found in the court papers. In litigation involving clinical research, one of the most examined and frequently attacked documents is the informed consent form, more so than might be seen in medical malpractice litigation.

Post-Trial Allegations

Given the many and varied parties and participants in a research study, contractual relationships in clinical trials are complex. Apart from the clinical trial agreement (CTA)--the primary contract between sponsors and investigators--other contractual relationships in this research setting have not received much attention; however, some are highlighted in the case of *Abney vs Amgen*, a Phase II trial involving participants with Parkinson's disease. The study was sponsored by Amgen and conducted at the University of Kentucky Medical Center in 2003. The intervention was a synthetic peptide called GDNF, a glial cell line–derived neurotrophic factor. The drug was administered via a catheter into the putamen of the brain.

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The informed consent form for this study stated that participants "may elect to continue treatment for up to an additional 24 months." This form also stated that the study could be terminated for a host of reasons, among them, if its risks outweighed its benefits. After six months, the study results were disappointing; although those on the active arm showed slight improvement, the results were statistically insignificant. Amgen decided to continue the study with all 34 patients receiving open-label GDNF. However, in September 2004, the company decided to stop the study because neutralizing antibodies had developed in several participants. Furthermore, data showed that brain lesions had developed in primates, and that the drug lacked efficacy.

Despite this disappointing information, many study participants believed that they had improved with this new, albeit experimental, drug. They believed that Amgen, by stopping the study and ending their access to the drug, had broken a promise to them, so they sued Amgen for breach of contract, promissory estoppel, and a breach of fiduciary duty. The breach of contract claim failed when the court ruled that Amgen, as the study sponsor, had a contract with the investigator and the university, but not with study participants. The estoppel and fiduciary duty claims were similarly unsuccessful, as the court found that Amgen made no direct promises to the participants that would create an estoppel situation, and that Amgen had no fiduciary duty to the participants to continue to provide them with the study drug.[7]

In this case, to the extent that the informed consent document should be seen as a contract, it was regarded as an agreement between investigators/institutions and participants, not between the participants and Amgen. Although this may hold in the United States, one might wonder if the result would be similar outside the U.S. borders. For example, would this result be the same in a jurisdiction where most sponsors prepare informed consent documents and submit them to RECs with very little input from investigators, as is uniformly the case in South Africa?

The TGN1412 Phase I trial at Northwick Park Hospital, London, has received global attention. The trial involved a humanized monoclonal superagonist of the CD28 T-cell surface receptor. Of the eight volunteers involved, two received placebo and six were given the active study drug. In what has been described as a cytokine storm, participants in the active arm became seriously ill after the drug was administered. Some developed temporary physical deformities, while others had more lasting adverse effects.[8]

Several queries have been raised in this study around the interval between administration of the drug amongst the volunteers, scientific review of a study that was possibly theoretically flawed, and the use of the mouse as a model for human physiology, given that the CD28 receptor differs significantly in its amino acid composition in mice and men. Fortunately, efficient and rapid treatment of the research-related injuries resulted in all but two volunteers experiencing a reasonable recovery. Two participants have some residual physical injury—malignancy in the one instance and loss of digits in the other.

This event took its toll on the sponsor, TeGenero, which has declared bankruptcy. The insurance policy for the study was valued at £2 million, and interim payments of £10,000 have been made to each of the affected volunteers. However, the total sum of money required for compensation for research injury amounted to £6 million. The CRO, PAREXEL, is now theoretically expected to cover the shortfall of £4 million.[9] This case remains unresolved at the time of this writing, and may indeed be the subject of litigation in the future to achieve some resolution.

Allegations in an International Context

International collaborative research (traditionally conducted by a sponsor from a developed country in one or more developing host countries) is a thriving and controversial global activity. In the litigation context, the Trovan case is a good example that raises complex questions about ethical relativism related to the exploitative conduct of research with compromised standards of care.

During a meningitis epidemic in Nigeria in 1996, Pfizer allegedly enrolled nearly 100 Nigerian children with meningitis to test the antibiotic trovafloxacin (Trovan) against ceftriaxone. The children in the control arm were given a suboptimal dose of ceftriaxone (33 mg/kg instead of 100 mg/kg). During the study, children in both arms were harmed. Eleven children died and others became deaf, mute, or sustained brain damage. Trovan has never been approved by the FDA to treat meningitis, and in June 1999 the FDA issued a warning that use of the drug could lead to liver toxicity and death. Trovan was withdrawn from European markets after reports of fatal liver disease.

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In the lawsuit arising out of the study, the plaintiffs' allegations and claims include violations of the Nuremberg Code, the Declaration of Helsinki, FDA regulations, and Article 7 of the International Covenant on Civil and Political Rights. In addition, claims have also been made regarding deficiencies in the informed consent process. The lawsuit alleges that Pfizer did not inform families that Trovan was an experimental treatment and failed to obtain an adequate informed consent. Damages in the amount of $9 billion (US) have been requested.[10,11] This case was scheduled to be heard in October 2007, but was not; the civil and criminal charges are still pending, and the case remains unresolved to date.

Class Action

In traditional medical care litigation, individual patients usually sue health-care professionals on a one-to-one basis. In the research context, however, Phase III trials may enroll hundreds of participants who are exposed to the same experimental agent and may likely sustain similar research-related injuries. As such, these participants are able to sue as a group, and the judgment or settlement will apply to the entire group.[1] The 30 families in the Trovan case in Nigeria were such a group, and their lawsuit was brought as a class action.[10,11]

Although not related directly to clinical research, the lawsuits against American Home Products, a Wyeth Pharmaceuticals subsidiary, represent another example of class action lawsuits and the magnitude of claims that are raised in them. The combination of drugs fenfluramine and phentermine for weight loss, commonly referred to as "fen-phen," was found to be associated with valvular heart disease and pulmonary hypertension at the Mayo Clinic in 1996–97.[12] Consequently, the FDA withdrew market registration of these drugs in 1997, essentially leading to the drug companies' involvement in lawsuits claiming a total of nearly $20 billion (US) in damages for the class of affected patients.[13]

Protection Against Litigation?

Most investigators depend on REC approval of their study to protect them against possible claims by aggrieved study participants. The informed consent document is also regarded as some protection and defense against litigation claims; however, this may

not always be the case. Many claims in clinical trial litigation have targeted and attacked both the informed consent document and the REC review process as faulty and inadequate. Such was the case in the Gelsinger litigation mentioned earlier.

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Further, in some cases, the courts may indeed take their own second look at the REC approval process, and the result could be substituting the REC decision with a stricter court decision. This occurred in the landmark case of *Grimes vs Kennedy Krieger,* where the plaintiffs were families who had been enrolled in a study to assess how effective varying degrees of lead paint abatement procedures were at protecting children from the harmful effects of lead exposure. The families argued that the study should never have been conducted because continuing to expose children to the harmful effects of lead paint was simply not justifiable on any grounds–scientific, ethical, or otherwise. The REC at Johns Hopkins had approved the study on the basis that its benefits outweighed the risks; this premise is what the Maryland courts reviewed in deciding that the REC risk assessment was negligent. The court replaced the REC judgment with its own, and further held that neither REC approval nor parental consent could protect investigators from liability.[1]

Avoiding Litigation

Clinical trials are scientifically, ethically, and legally challenging. This article has provided a brief non-lawyer's perspective on the myriad challenges that may arise during litigation involving clinical trial research. All of the research roleplayers are bound to the research by complex regulatory and contractual relationships. To avoid litigation as best they can, all of these players must be aware of and exercise their research responsibilities with diligent care and caution. Investigator responsibility in clinical trials demands a thorough understanding of the protocol, the consent document and process, and the clinical trial agreement. The REC's responsibilities include a thorough scientific review of protocols with particular attention paid to the risk-benefit ratio of the experimental agents being studied. In addition, the REC must attend to the informed consent documents, CTAs, insurance, and other related documents with careful attention to detail.

The integrity of all research team players and stakeholders in the clinical trial industry is imperative.

In some countries, like South Africa, legal representatives on RECs have a crucial role to play in assessing CTAs, informed consent documents, and insurance certificates. In particular, in high-risk studies, it is important to assess the adequacy of insurance coverage for the research with respect to the number of participants to be enrolled and the eventuality of research-related injuries. Further, the integrity of all research team players and stakeholders in the clinical trial industry is imperative. The failure of any of these to adhere to national and international research regulations and guidelines, of which there are many, will only serve to invite, rather than avoid, the prospect of litigation in clinical research.

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Keymanthri Moodley, MBChB, DPhil, has 20 years of medical experience, predominantly in family medicine, and has been involved in clinical trial research for the past seven years. Currently she is founding director of the Bioethics Unit–Tygerberg Division at the University of Stellenbosch. She is vice chair of the research ethics committee at the university, and has been conducting good clinical practice training for the past six years. She also is the managing member of a private clinical trial company, Cape Clinical Trials, and can be reached at km@sun.ac.za.