Litigation in Clinical Trials

Introduction

Litigation in clinical medicine is a well established phenomenon. Litigation in clinical trial research is a relatively new development that is expanding globally.

In the context of research, the investigator-participant relationship differs significantly. In therapeutic research where specific investigational products are tested on participants with appropriate diseases, the study participant may stand to benefit to a certain degree. In non-therapeutic research on healthy participants or in placebo controlled therapeutic trials where the participant may be randomized to the control arm of the study, there may be minimal benefit for the participant. Under such conditions, the benefit to science and society is bound to be significant enough to render the research participant a means to an end.

Furthermore, there is a perception that in industry sponsored clinical trial research investigator goals may not be aligned with participants’ best interests. As a result a precarious relationship exists between participant and investigator in which participants require special protection of their rights. When this fails to occur, litigation is likely to enter the world of clinical trials. In the research setting, litigation differs significantly from medical malpractice litigation in many respects – naming of defendants, allegations and financial settlements especially where class action is invoked (Mello, 2003).

Defendants

Unlike medical malpractice litigation where the defendant usually is an individual health care 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)/individual REC members, contract research organizations (CROs), bioethicists and regulatory agencies. In the case of Weiss vs Solomon, a patient 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. The hospital was included because the hospital REC approved a deficient IC form (Shaul, 2005). In the gene therapy trial of 19 year old Jesse Gelsinger (Sibbald, 2001), several defendants were named. The 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 impact on any combination of role players.
Allegations

A broad spectrum of allegations may occur in clinical trial litigation. Some of these may pertain directly to the conduct of the trial while others may involve issues that arise after the trial such as compensation for research injuries and post trial provision of treatment. While most allegations are resolved in national settings, some allegations take on an international perspective.

Trial related allegations

1. Informed Consent (IC) Deficiencies

Informed consent is equally important in research and clinical care. However, standards for informed consent in research are generally higher than those upheld in clinical care. In the context of the doctor-patient relationship, it is essential to inform the patient of risks that are material to his/her decision-making. In clinical trials, all risks are disclosed together with the probability of each risk occurring. This will include the risk of death irrespective of how small that might be.

This was illustrated in the Nicole Wan case in 1999. This healthy 19 year old University of Rochester student was enrolled in a research study requiring bronchoscopy and alveolar cell lavage in 1996. She required large doses of the anaesthetic 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 hospital where she died after a cardiac arrest. Her postmortem revealed that she had received 1200mg of Lignocaine instead of 300mg specified in the protocol. Furthermore, the consent form did not mention the possibility of death as a risk of the procedure (Day, 1998).

Jesse Gelsinger had a partial deficiency of the enzyme ornithine transcarbamylase. He died after a gene infusion carried by an adenovirus vector. An enquiry into his death revealed that adverse events detected in other human trials and in prior animal studies were not included in the IC form (Sibbald, 2003).

In the Hexamethonium study in 2001 at Johns Hopkins University several legal loopholes were found in the IC process. This drug was previously used to treat hypertension, but was found to be ineffective and was deregistered for that purpose by the Food and Drug Administration (FDA). Hexamethonium was administered by inhalation to healthy volunteers including a 24 year old employee of the Asthma and Allergy Centre at Johns Hopkins, Ellen Roche. She died days after the study drug was administered to her. The investigation revealed that the IC form was deficient in many respects. Hexamethonium was described as “a medication that has been used during surgery as a part of anaesthesia; this is capable of stopping some nerves in your airways from functioning for a short period” (Steinbrook, 2003). All the side-effects of hexamethonium were not 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 death in this study, was not mentioned. The experimental nature of the drug was not clarified, instead it was referred to as “medication” (Steinbrook, 2003).
2. Conflict of Interest

Failing to disclose a conflict of interest in the IC form may result in a charge of fraud against investigators (Mello, 2003). Such an allegation is financially more viable than claims that might arise from simple deficient consent processes. In the Jesse Gelsinger case the University was to receive an ownership stake in Genovo – the sponsor – in lieu of funding of the gene transfer research program. Both the university and the doctors involved had equity and financial interests with respect to the viral vectors used (Sibbald, 2001). This conflict of interest was not disclosed in the IC process and form. An undisclosed conflict of interest implies that the IC process is not truly informed.

The pivotal role of the IC process in clinical trials is underscored by a host of allegations related to its deficiency. In cases of legal dispute, one of the documents reverted to most frequently is the IC form.

Post-trial allegations

1. Breach of Contract – Post-trial provision of treatment

Contractual relationships in clinical trials are complex. Apart from the clinical trial agreement (CTA) that is an obvious contract between sponsors and investigators, other contractual relationships have not received much attention. These relationships are highlighted in the case of Abney vs Amgen - a phase 2 trial involving participants with Parkinson’s disease. The study was conducted at the University of Kentucky Medical Centre in 2003 and was sponsored by Amgen. The intervention was a synthetic peptide called GDNF – glial cell line derived neurotrophic factor. The drug was administered via a catheter into the putamen of the brain. The IC form stated that participants “may elect to continue treatment for up to an additional 24 months”. The form also stated that the study could be terminated if risks outweighed benefits or for a host of other reasons. After 6 months 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. By September 2004, Amgen decided to stop the trial as neutralizing antibodies had developed in several participants. Furthermore brain lesions had developed in primates and the drug lacked efficacy. Many participants believed that they had improved with this new drug. They believed that Amgen had broken a promise to them on the basis of a breach of contract, promissory estoppel and a breach of fiduciary duty. The court ruled that the sponsor had a contract with the investigator and the university, not with participants. The estoppel claim was unsuccessful as the sponsor had made no direct promises to the participants and finally, the sponsor had no fiduciary duty to the participants (Mello, 2007). Clearly, from a legal perspective the informed consent document represents a contract between investigators/institutions and participants – yet most sponsors prepare IC documents and submit them to RECs with very little input from investigators.
2. Compensation for research related injuries

The TGN1412 phase 1 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 8 volunteers involved 2 received placebo and 6 participants were given the active drug. In what has been described as a cytokine storm, those participants in the active arm became seriously ill after the drug was administered. Some participants developed temporary physical deformities while others had more lasting effects such as the loss of digits (Mayor, 2006). Several queries have been raised in this study: the interval between administration of the drug amongst the volunteers, scientific review of a study that was possibly theoretically flawed, 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. Efficient and rapid treatment of research related injuries resulted in all but 2 volunteers experiencing a reasonable recovery. Ryan Wilson and David Oakley remain with residual physical injury – malignancy in the one instance and loss of digits in the other. The sponsor Tegenero has declared bankruptcy. The insurance policy for the trial was valued at 2 million pounds. Interim payments of 10,000 pounds each have been made to volunteers. However, the total sum of money required for compensation for research injury amounted to 6 million pounds. The CRO, Parexel, is now theoretically expected to cover the shortfall of 4 million pounds (Steinbrook, 2006). This case remains unresolved.

Allegations in an International Context:

- Violation of International Human Rights

International collaborative research (traditionally conducted by developed sponsor countries in developing host countries) is a thriving and controversial global activity. The Trovan case raises complex legal questions. It also revisits fundamental questions of ethical relativism related to 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 100 children in the control arm were given 33mg/kg of ceftriaxone instead of 100mg/kg – a suboptimal dose. Harm was caused to children in both arms. Eleven children died and others became deaf, mute or sustained brain damage. Trovan has never been approved by the FDA to treat meningitis. In June 1999, the FDA issued a warning that use of the drug could lead to liver toxicity and death. The drug was withdrawn from European markets after reports of fatal liver disease. Plaintiff 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 IC process. It is alleged that Pfizer did not inform families that Trovan was an experimental treatment and failed to obtain IC. A lawsuit has been filed for $9 billion (Lenzer, 2006; Lenzer, 2007). The case remains unresolved to date.
Class Action

In traditional clinical care litigation individual patients sue health care professionals on a one to one basis. Phase 3 trials enroll thousands of participants who are exposed to the same experimental agent and hence may sustain similar research related injuries. As such, these participants are able to sue as a group and the judgement or settlement will apply to the entire group (Mello, 2003). The 30 families in the Trovan case in Nigeria represent an illustration of this type of class action (Lenzer, 2007).

REC Approval – adequate protection against litigation?

Most investigators depend on REC approval for legal immunity against possible claims by participants. The IC document is also regarded as protection against litigation. However, this may not always be the case. Many legal claims in clinical trial litigation have faulted the REC review process. In some cases, REC decision-making may be substituted 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 effectively varying degrees of lead paint abatement procedures could protect children from the harmful effects of lead exposure. The families argued that the trial should never have been conducted as continuing exposure of children to harmful effects of lead paint was not justifiable. The REC at Johns Hopkins had approved the study on the basis that the benefits outweighed risks. Maryland’s highest court decided that the REC assessment was negligent. The court replaced the REC judgement with its own judgement. The court held that neither REC approval nor parental consent could protect investigators from liability (Mello, 2003).

Avoiding Litigation

Clinical trials are scientifically, ethically and legally challenging. All role players are bound by complex contractual relationships. Investigator responsibility in clinical trials demands a thorough understanding of the protocol, the consent document and the clinical trial agreement. REC review of protocols must include a thorough scientific review with particular attention to the risk benefit ratio of experimental agents. In addition, the informed consent documents must be reviewed with careful attention to detail. The legal representative on RECs has a crucial role to play in assessing CTAs, IC documents and insurance certificates. In particular, in high risk studies, it is important to assess if insurance cover is adequate for the number of participants that will be enrolled and the eventuality of research injuries. Integrity of all team players and stakeholders in the clinical trial industry is imperative. Failure to adhere to national and international research regulations and guidelines, of which there are many, invites the prospect of litigation.