Does litigation raise standards of care in clinical research?

Recent high-profile lawsuits seeking redress on behalf of subjects, who died or were injured as a result of taking part in studies, have caused shockwaves throughout the pharma and clinical research industry. But do such cases really act as a deterrent to bad research practices? **Dr Douglas Mackintosh** and **Dr Stephen DeCherney** debate the issues

Healthy hunting? Why the 'junkyard dog' is a necessary protection

Henry Blauer at Columbia University. Tony LaMadrid at UCLA. Kathyn Hamilton at Fred Hutchinson. Nicole Wan, University of Rochester. Gage Stevens at the Children's Hospital Pittsburgh. Ellen Roche at Johns Hopkins University. What do these people have in common?

They all consented to taking part in a clinical study. Yes. They were all screened for inclusion criteria. Yes. They all died while taking part in a study. Yes. With hindsight, these studies were dangerous and should not have been conducted. Yes. We have learned from mistakes made during the trials that caused their deaths. Not necessarily.

Clinical studies may cause great harm. Until 1980, most US drug trials were conducted on prisoners. Now most of them are conducted on – presumably – well-informed volunteers who become subjects after carefully weighing up, potential risks and benefits. There is supposed to be a system of checks and balances in place within and across studies and institutions to protect subjects.

Researchers, principal investigators, pharmacists and study coordinators, have all pledged not to harm study participants and to consider their well-being above all else. Institutional review boards (IRBs) scrutinise protocols, amendments, investigator drug brochures, consents, SAEs and periodic drug safety reports. The FDA and National Institutes of Health (NIH) have implemented regulations and other procedural safeguards to protect subjects. An organised body of knowledge called good clinical practice has evolved, in part, to protect subjects. But are these measures enough?

Subjects are still injured while taking part in studies. Adverse events may be caused by the study drug, concomitant drugs, study procedures, care provider negligence, subject negligence, progression of the disease being treated in the study, new diseases and progression of previously existing diseases not being treated with the study drug.

Study-related injury, which may also include adverse events, is difficult to identify and many investigators, institutions and sponsors would prefer not to be financially responsible for the care of subjects who have suffered medical injury during a study, or for their compensation. The situation is not dissimilar to routine medical malpractice except that an investigational drug is involved, as well as other study-related tests and procedures.

To err is human, but some mistakes are preventable. Errors caused by negligence, particularly gross negligence, must be studied and actively prevented. What are the appropriate mechanisms, incentives and disincentives, for preventing errors and compensating victims for dangerous studies and the resulting injuries? If you ask a clinician this question, he or she will suggest either: there are already enough internal quality control mechanisms and external bodies to protect patients; or

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investigators simply need more training, perhaps compulsory training and certification. But ask a trial attorney and he or she will say there needs to be successful, well-publicised litigation to serve as a deterrent.

I tend to side with the trial attorneys, even the avaricious ones. Despite their greed and bad manners, they keep the game honest in an arena now teeming with clinical studies. You don't have to agree with their motives, or even their tactics. You just have to believe there should be a 'junkyard dog' cruising the streets ready to fight your corner should all other protective mechanisms fail to ensure subject safety.

Subjects who are injured deserve to be compensated for care-provider negligence, poor study design, unexpectedly toxic study drugs and gross violations of GCP standards and guidelines that result in injury. Their injuries should be treated, their pain and suffering addressed. Negligent parties should be dissuaded from other behaviour that is below standard. Clinical trials litigation, when it is neither frivolous nor discriminatory, serves this purpose. It means that care providers, CROs and sponsors perform better than they would in the absence of this protective mechanism.

This point is reinforced by Alan Milstein, the king of the small but growing band of clinical trial attorneys. He comments: "As to whether litigation has improved the ethics of research, I would say that litigation has certainly caused the community to focus on the ethics involved in such research. The Gelsinger case is really the moving force and I always emphasise that it was not the litigation but the killing of this 18-year-old innocent that has caused the world to sit up and see what was happening. Litigation thus is only the public airing of the wrongdoing that had occurred. The truth is the regulatory process is broken, ineffective and controlled by the industry. So litigation, which results in publicity and media reports and various appearances by the principals, is really the only means of change."

While I do not believe that civil litigation is the only mechanism capable of improving clinical trials, it is an important weapon in our fight to protect human subjects and prevent medical injury. GCPj

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Hunting the wrong quarry – why the market works best to maintain GCP

Perhaps I should preface my response to Dr Mackintosh's interesting arguments by mentioning that some of my best friends are trial lawyers. Honestly, my brother-in-law is such a fellow and a fine gentleman too. In fact, I have testified, as an expert, against other physicians when I felt their negligence was so egregious someone had to make a stand. In other words, I believe that appropriate litigation has its place as a very downstream check against negligent behaviour that results in harm – the definition of malpractice in the US, by the way.

First, however, let us establish a pattern of facts, as the lawyers would say. There is one similarity among the victims' cases that Dr Mackintosh has failed to point out, namely that in each one the research was performed in an academic setting, usually a university hospital. To the best of my knowledge, there have been no suspicious deaths among research subjects outside a university. Perhaps the most dangerous research only takes place in those institutions but even if this is the case there should have been appropriate informed consent – and had there been appropriate consent there would have been no litigation.

What about the tens of thousands of other investigator sites outside academia? Most of them are watched carefully by hordes of clinical research associates employed by sponsor pharmaceutical firms. While the FDA has threatened to shut down major research programmes and – in the cases of Johns Hopkins and Duke – carried out the threat, these programmes will generally continue with business as usual. (To their credit both universities instituted more stringent oversight of their programmes as a result of the FDA's measures.) In a sense, the federal government has left it to trial lawyers to punish the perpetrators with civil actions.

By contrast, the market will punish a pharma company whose business practices are unethical. If the FDA delays the clearance of a new drug because of unreliable data, millions of dollars are lost for

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every day of delay. A firm may see its share value plummet as a result of the delays to which the stock market is exceptionally sensitive.

I think the cases highlighted by Dr Mackintosh were really caused by the disparity between standards in academic settings and in private, for-profit environments. I have been an investigator in both for many years.

Academic settings are much more relaxed. For example, I have witnessed many trials that could not even show the primary endpoint. They were deemed 'exploratory' or 'pilot' studies 'looking for trends'. The logic of these is spurious at best. Should any human be subjected to experimentation when the benefits of doing so are ill-defined? In the for-profit world, cost stops these studies from being carried out.

No pharmaceutical company can afford to waste money on trials that do not clearly define a physiological principle let alone a therapeutic point. I have witnessed investigator-driven, pharma-industry-funded studies that were cleaned up by the pharma firm.

Even with occurrences of malpractice in the private sector, it is unclear to me how a case that takes two or three years to wind through the courts helps to improve the practice of clinical research. Moreover, I am not sure whom the target of the litigation should be. Who is the ultimate defendant in these cases? From a legal standpoint, all parties contributing to the negligence would be held responsible. From a moral standpoint, it is less obvious.

So do I completely disagree with Dr Mackintosh? Not at all. There is a place for civil litigation in clinical research just as there is in ordinary clinical practice. I do not, however, think there is widespread negligence among investigators and to behave as if it were true by encouraging trial lawsuits would be foolhardy and counterproductive. GCPj

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Head-to-head

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