

Chapter 15

Legal and Ethical Issues of Justice: Global and Local Perspectives on Compensation for Serious Adverse Events in Clinical Trials

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Abstract A 78-year-old Chinese woman joined a clinical trial sponsored by a pharmaceutical company. Unfortunately a serious adverse event (SAE) occurred. The sponsor paid for the cost of the medical care arising from the SAE, but refused the family's request for compensation. The family then sued the company and the hospital in Beijing. Although the SAE was related to a complication of lower extremity angiography and not the drug itself, it was a direct consequence of participating in the trial. According to Good Clinical Practice, a set of regulations promulgated under Chinese law, "the sponsor should provide insurance to those human subjects who participate in clinical trials, cover the cost of treatment and the corresponding economic compensation for the occurrence of the harm or death associated with the trial" (SFDA in Good clinical practice. State Food and Drug Administration, 2003: art. 43). The court ordered the trial sponsor to provide a translation of the company's insurance policy, so that the court could understand the amount of compensation available to the patient under the policy, but the sponsor never surrendered either the documentation or a translation. Consensus was never reached about the amount of compensation due to the patient through negotiation with the hospital, the company and the family. The litigation ended after nine hearings and five long years. This chapter provides an ethical analysis of the case relative to at least three areas of risk of exploitation when a major, international pharmaceutical company sponsors clinical research in a country with an immature legal system and where research participants have limited resources.

Keywords Clinical trial • Serious Adverse Event (SAE)
China • Global research • Justice • Insurance

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Areas of Risk of Exploitation

There are at least three ways in which this case illustrates the risk of exploitation.

The principle of justice requires that the benefits and burdens of research be distributed fairly. This means that participants who are injured during the research should be compensated fairly for their injuries. The present case demonstrates the main risk of exploitation during the process of an individual research participant's litigation. Although individuals may be compensated, litigation is costly and time-consuming. Studies have found that approximately 50% of the sums recovered from tort lawsuits in high-income countries (HICs) do not reach the injured parties but instead go to attorney fee payments and other costs. Legal barriers such as the assumption of risk, contributory negligence and government immunity may discourage litigation by injured research participants or preclude recovery in whole or part (Resnik et al. 2014).

Second, this case illustrates the risk of exploitation due to the considerable variation in regulations across various countries, which results in inconsistent compensation for the victim of a serious adverse event (SAE). Regarding the payout amount for compensation, trial sponsors might approach the amount differently for human research participants who suffer the same SAEs in different countries. This suggests that the values of justice may not be fulfilled, as there should be no double standards in the compensation for SAEs. While there is no data publicly available about variations in payment for SAEs, this case raises the suspicion that equal and just compensation in global studies is not being achieved, or at least not in all cases. Exploitation occurs when different patients suffer the same harm or injury, but do not receive equal compensation (or at least compensation adjusted to amounts based on average incomes in the countries concerned).

The third risk of exploitation derives from the inequality in access to resources for litigation between individual research participants and pharma sponsors. In this case the company exploited its position of litigatory strength. It did not cooperate with the local court, in that, for example, it did not supply either the original of the insurance contract or a translation into Chinese. In addition to being a failure to comply with the court's request, this delayed the legal process.

Background

Xarelto® (rivaroxaban) or BAY 59-7939 is an oral tablet (factor Xa inhibitor), taken once a day, intended for prophylaxis of deep vein thrombosis (DVT) and the prevention of atrial fibrillation, cardiac thromboembolism and cerebral infarction. The company's application "On the BAY 59-7939 international multi-centre phase III clinical trial" was submitted to China's State Food and Drug Administration

(SFDA) in October 2005 and approved in February 2006. The institutional review board (IRB) of a hospital approved the trial based on the application. Being a global clinical trial, the hospital was invited as the leading centre. The trial sponsor signed a contract with the hospital.

The Case

A 78-year-old woman came to hospital for knee replacement surgery. During her index hospitalization in 2006, she was invited to join this clinical trial. Her daughter was with her at the time of recruitment, and they both agreed to her participation. The knee replacement surgery was conducted on 24 October 2006. In accordance with the protocol, she took the daily tablet, intended for prophylaxis of DVT and the prevention of atrial fibrillation, cardiac thromboembolism and cerebral infarction. She was enrolled from 23 October to 6 November 2006. The research protocol required the patient to undertake double lower-limb vein angiography in order to test for thrombus formation. An SAE occurred after venous angiography. The patient suffered chest tightness, shortness of breath, palpitations, cough, sweating, a very weak pulse, blood pressure dropping to 60/40 mm HG and shock. The patient regained consciousness three hours after resuscitation. The hospital's principal investigator judged this complication to be an SAE and completed the SAE report form on 15 February 2007. The SAE was also reported to the China State Food and Drug Administration on the same day.

The total expenses of the medical treatment caused by the SAE were CNY 3296.17 (approximately USD 420 in 2006), all of which the trial sponsor paid. Considering the patient's suffering and the adverse effect on her recovery of knee function, she and her family desired compensation for the limitations the SAE had imposed on her life. The patient and her family knew that the sponsor had compensation insurance for the study. The investigator reminded the patient of this, and they found relevant information in the informed consent form.

In the section entitled "Patient Notice", the consent form read, "if a subject involved in this trial is injured during the study, the insurance company will pay correspondingly". Based on the consent form, and the study investigator's explanation, the patient knew that the trial sponsor had purchased global insurance for this multi-centre clinical trial. When the patient and her family requested compensation from the hospital and the pharmaceutical company, the company refused. Despite extensive discussions, the three parties could not reach consensus. After failure to agree on a compensation amount, the sponsor and the hospital were summoned to the Beijing Chaoyang Court by the plaintiff in 2008.

Procedure for Compensation Claim in China

Usually in China, if a plaintiff is injured and claims compensation, the court will require the plaintiff to consult with a third party to evaluate the nature and degree of the injury. Based on this evaluation, the court can then make a judgement about the seriousness of the injury, and determine an amount of compensation. In this case, the children did not want to expose their elderly mother to the pressure of visiting the evaluation centre and having to wait a long time for a result that she might not be satisfied with anyway, so they decided to spare their elderly mother this ordeal. The family did not file a suit as a lawsuit based on infringement of rights or as a suit of tort, but filed as a “dispute of contract”.

The Source of Disagreement

The sponsor argued that there was an agreement between themselves and the hospital to carry out the trial of a new drug, and hence a contractual relationship between the company and the hospital, but there was no contractual relationship between the company and the patient plaintiff. In contrast, the plaintiff argued that the hospital had clearly informed the patient (research participant) that the hospital was only a representative of the trial sponsor, and further that the research participant had been informed that the company had entrusted/endorsed the hospital to sign the contract with trial participants. On these grounds, the plaintiff declared that a contractual relationship existed between the plaintiff and the company. The Chaoyang Court ultimately accepted the plaintiff’s claim as a dispute of contract.

Having accepted the suit, the court requested the parties to provide the relevant documents. It repeatedly requested the company to provide a copy of the insurance contract, and explained this requirement to the company, but the company resisted and did not submit the insurance contract. The court also asked the hospital for the insurance contract, but the hospital responded that it had been unaware that it should request that documentation. Similarly, the hospital ethics committee had not required confirmation of an insurance contract at the time the protocol was approved. The hospital argued that it had signed a clinical trial contract with the company, which had declared that it had purchased special insurance to cover economic loss by the subjects participating in the study, including any harm caused by the drugs. The third page of the participant information sheet for the study stated: “Adverse drug reactions related to angiography include angiography reaction, such as skin reaction; some will imply allergic reaction, such as anaphylactic shock”. Thus an adverse event from the double lower-limb vein angiography was included.

The plaintiff then requested the hospital ethics committee to seek help from the SFDA, but the committee were informed that the SFDA did not have this document

either. In short, no one but the company had access to a clear description of the amount of compensation during the earlier stages of the case.

Later in the court process, the pharma company provided Chaoyang Court with certification of insurance purchased from a German provider, certifying that the company purchased insurance effective from January 1, 2002, which covered the study overseas and participants from all countries. Each person's maximum insurance was approximately 500,000 Euro. (Chao Min Chu Zi 2009).

The court asked the company to provide a Chinese version of the insurance contract, but the company refused. After several requests, the court, the plaintiff and her family were informed that it would take a long time to prepare such a translation and that it would be too expensive (estimated cost CNY 20,000, approximately USD 3,000 at that time).

This meant that the available documentation – namely, the consent form and insurance contract – included no clear description of the exact amount of compensation, nor how to compensate for different situations, types of injury, different countries, etc. When the plaintiff claimed EUR 150,000 compensation, the company argued that there was no reasonable basis for such a claim.

Though no specific criteria were provided about the amount of compensation, the civil judgement included a clause referring to the insurance company's view that where the company was responsible for the compensation of subjects, the insurer should provide the compensation based on the requirements of the local laws where the injury occurred (Chao Min Chu Zi 2009). The pharmaceutical company requested a non-public hearing for the appeal, which made information unavailable. The plaintiff explained that she was persisting with her appeal as she suspected that there was an unfair clause in the insurance contract and that there was an unequal description of compensation for HICs and LMICs.

After five years, the lower court's judgement was issued in February 2013. The Beijing Chaoyao Court determined that according to the Chinese Good Clinical Practice regulations, the company should compensate the plaintiff with EUR 50,000. However, the plaintiff did not accept this, and appealed to the Beijing Second Middle Level Court. That court rejected the appeal.

In summary, between 2009 and 2011, nine hearings were held. The final conclusion came out in February 2013. The entire process of litigation and appeal lasted for five years. Compensation of EUR 50,000 euros was paid directly by the company, not by the insurance company. This suggested that the process of SAE compensation was dealt with internally within the company, rather than through a formal procedure that involved the insurance company.

Due to the SAE and consequent extended hospitalization, the patient was placed on strict bed rest, even though rehabilitation from the original knee replacement surgery would have required her to move. Her dream had been to travel abroad after the surgery, but participating in the trial delayed her rehabilitation from the surgery.

Update

It was reported from Berlin on 4 May 2015, that the company's once-daily oral anticoagulant BAY 59-7939 (rivaroxaban) had been approved by China's State Food and Drug Administration for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors (Bayer 2015). Additionally, the administration has approved BAY 59-7939 for the treatment of DVT and the reduction of the risk of recurrent DVT and pulmonary embolism following acute DVT in adults. Since 2009, BAY 59-7939 has been available in China for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery.

Lessons Learned & Recommendations

- Though the capacity for human research participant protection and ethics review have been improved in China in recent years, this case shows that some matters may have been neglected, especially access to the insurance contract for compensation. In this case, all three stakeholders should strengthen their sense of responsibility and learn this lesson: the hospital's ethics review committee did not fulfil its responsibility to request the company to provide the insurance contract. The SFDA needs to develop a working system which ensures that the pharmaceutical company sponsoring a trial prepares and submits to the ethics review committee relevant documents such as the insurance policy as a requirement.
- While both the local Chinese Good Clinical Practice regulations and the Guideline for Good Clinical Practice of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH 1996) have provisions about compensation, it is hard for an individual research participant to negotiate and reach consensus with individual companies. For example, article 43 of the Chinese GCP (SFDA 2003) addresses compensation, but clearly places the responsibility on the shoulders of the sponsor.
- The prolonged processes involved in the interpretation and application of the law also contribute to potential harm and exploitation of trial participants and their families. In this case, the lawsuit started in 2008 when the plaintiff was 79 years old and ended when she was 85. Her dreams of travel after the knee replacement surgery were shattered.
- Bringing a legal case always involves costs for the plaintiff, which have to be advanced at least until the court reaches its finding or insurance is paid. It is often impossible for vulnerable populations in research to provide fees to lawyers and courts. (This case was an exception.)

- Within China, as this case illustrates, an academic dialogue is needed on the nature of the relationship between individual human research participants and a trial sponsor. During medical treatment, patients and doctors form a fiduciary relationship, as well as a contractual relationship. There is academic discussion of the doctor-patient relationship. However, there is not yet an academic discussion about the nature of the relationship between research participant and trial sponsor.
- This case calls into question whether compensation for injury should be a set amount, an amount based on an individual's economic situation, or an amount based on a country's economic situation. Regarding the amount of compensation to an individual research participant with an SAE during a global clinical trial, ethicists need to address the ethical challenge of a double standard.
- One final lesson relates to the exploitation of a less mature legal system. China, like many other middle-income countries, lacks lawyers and legal teams who are able to provide support in litigation with a pharmaceutical giant.

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