Insurance & Compensation in Clinical Research~ comparative and Asian perspectives

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Presentation Outline

- What Should Clinical Trial Insurance Cover?
- International Guidelines on insurance/ compensation/protection
- Current Regulations in Europe, UK, USA
- Asian Countries (South Korea, Taiwan)
- Summary & Suggestion

Clinical Trial Litigation in Nigeria
The "Trovan" Case (2009)

The Washington Post

Pfizer Reaches Settlement In Nigerian Drug-Trial Case

By Joe Stephens
Washington Post Staff Writer
Saturday, April 4, 2009
Pfizer has reached a broad agreement to pay millions of dollars to Nigeria's Kano state to settle a criminal case alleging that the drug company illegally tested an experimental drug on gravely ill children during a 1996 meningitis epidemic.

The details remain private, but sources close to the negotiations said the total payments -- including those to the children, their families, the government and the government's attorneys -- would be about $75 million under the current settlement terms. Other details, including how the money will be distributed, are to be worked out within weeks.

Nigerian authorities say Pfizer's infamous trial of the antibiotic Trovan killed 11 children and disabled scores more. The amicable agreement, it means both parties need to give and take."

Nigerian lawyers close to the negotiations, held over the past year in Nigeria, London and Dubai, told The Washington Post that Pfizer set a number of conditions, specifics of which remain undisclosed.

In 2007, Nigeria's federal government and the state of Kano filed four civil and criminal actions against Pfizer and 10 individuals, including former Pfizer chief executive William C. Steere Jr. The actions sought $9 billion in restitution and damages, and included 31 criminal counts, including homicide.

"We have made good progress in the negotiations," Pfizer said in a formal statement issued yesterday from its corporate headquarters in New York. "There are still several important issues that need

Reference: The Washing Post 4th April 2009, http://articles.washingtonpost.com/2009-04-04/news/36807353_1_trovan-pfizer-chief-executive-william-c-steere

Clinical Trial Litigation in Nigeria
The "Trovan" Case (2009)

Background

- Drug Manufacturer: Pfizer
- Testing of antibiotic — Trovan for treatment of Meningitis epidemic starting from 1996.
- **11 Children died and about 200 injured.**
- **Litigation starts since 2001.**

Allegation investigated

- Trial did not conform to US patient-protection standards
- The oral form of the drug used in the trial had not been previously tested in children
- No signed consent forms for the children
- Reliance on falsified ethics approval letter
- Researchers also gave children substandard dose of a comparison antibiotic

Settlement

- USD 75million

Drug maker files for Insolvency after serious adverse effect to six human subjects ~ the TeGenero Case (2006)

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Drug maker files for insolvency

The German firm that produced a drug at the heart of a disastrous clinical trial that left six men seriously ill has declared itself insolvent.

Parexel carried out the trial for TeGenero

TeGenero, a German pharmaceutical company, said it could not continue in business.

Because of the fallout from the UK trial, it was impossible to attract investment, TeGenero said.

Claims for compensation arising from the trial will continue to be handled by TeGenero's insurers.

Parexel, a clinical research organisation, carried out the trial on behalf of TeGenero.

Six previously healthy men who took part in the trial of the drug, TGN1412, suffered multiple organ failure.

The Medicines and Healthcare products Regulatory Authority (MHRA) said Parexel failed to follow proper procedures.

Reference: *BBC News 4th July 2006*, http://news.bbc.co.uk/2/hi/health/5146692.stm

Drug maker files for Insolvency after serious adverse effect to six human subjects ~ the TeGenero Case (2006)

Background

- Drug manufacturer: TeGenero, A German Pharmaceutical Company.
- Clinical Research Organisation, Parexel, carried out the trial on behalf of TeGenero.
- Phase I trial for testing of drug —TGN1412.
- **Six subjects participating the trial suffered multiple organ failure in the UK trial**.
- The Medicines and Healthcare products Regulatory Authority (MHRA) said Parexel **failed to follow proper procedures**.

Development

- TeGenero **went into insolvency after the event**.
- Claims for compensation arising from the trial continues to be handled by TeGenero's insurer.

What Should Clinical Trial Insurance Cover?
(Karlberg & Speers 2010)

- Professional negligence in the course of conducting clinical trials.
- Product liability, in case a product under investigation causes injury.
- No-fault liability – intended to provide compensation to research participants, regardless of liability, in the event of their suffering a significant and enduring injury (including illness or disease) which, on the balance of probabilities, is attributable to their involvement in the clinical trial.

International Guidelines on Insurance & Compensation

- **Declaration of Helsinki**

  Art. 14

  … The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and **provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.** The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

International Guidelines on Insurance & Compensation

- **International Ethical Guidelines for Biomedical Research** (Councils for International Organizations of Medical Sciences, CIOMS)

  Guideline 19: Right of injured subjects to treatment and compensation

  Investigators should ensure … research subjects who suffer injury as a result of their participation **are entitled** to free medical treatment for such injury and to such financial or other assistance **as would compensate them equitably for any resultant impairment, disability or handicap.** In the case of death as a result of their participation, their dependants are entitled to compensation. **Subjects must not be asked to waive the right to compensation**.

International Guidelines on Insurance & Compensation

Guideline 19 commentary

Obligation of the sponsor with regard to compensation.

- Before the research begins, **the sponsor**, whether a pharmaceutical company or other organization or institution, or a government (where government insurance is not precluded by law), **should agree to provide compensation** for any physical injury for which **subjects are entitled to compensation**, or **come to an agreement with the investigator** concerning the circumstances in which the investigator must **rely on his or her own insurance coverage**. … **Sponsors should seek adequate insurance against risks to cover compensation**, independent of proof of fault.

International Guideline on Insurance & Compensation

- **ICH E6-GCP**

  5.8 Compensation to Subjects and Investigators

  5.8.1 If required by the applicable regulatory requirement(s), **the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial**, except for claims that arise from malpractice and/ or negligence.

Clinical Trials Insurance in selected countries
(Swik 2009)

- **Compulsory insurance** (examples):

  Germany (accident type), Czech Republic (liability type), France (liability), Netherlands (accident), Japan (liability), New Zealand (liability), Austria (accident), Greece (liability), Portugal (liability), Spain (liability), Poland (liability)

  → **sum of insurance often not fixed by the law**

- **Non compulsory insurance** (examples, changes possible):

  Great Britain (liability, special regulation), USA (liability), India (liability), Luxembourg (liability), Mexico (liability)

  →**compulsory insurance often to be found**

  →**if not compulsory, coverage is given in existing normal liability policy frequently**

Clinical Trial Insurance in Europe

- Directive 2001/20/EC (on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)

Article 3:Protection of clinical trial subjects

2. A clinical trial may be undertaken only if, in particular:

(f) **provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor**.

- Insurance fees have increased by 800 % for industry sponsors since its implementation.

Clinical Trial Insurance in Europe

- The Directive 2001/20/EC introduced an 'obligatory insurance/indemnity', which has substantially increased the costs and administrative burden of conducting clinical trials, but there is no evidence that the number of damages, or the amount, has increased with the entry into force of the Directive.
- The Directive has had many direct effects on the cost and feasibility of conducting clinical trials which … have led to a decline in clinical trial activity in the EU.
- The European Commission held two public consultations, several meetings, and a large stakeholder workshop for the legal revision of the Directive 2001/20/EC.
- A new proposal was introduced in July 2012.

Clinical Trial Insurance in Europe

- **A New proposal** (2012) for a "**REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL — on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC**"

  - **Chapter XII**- Damage compensation, insurance and national indemnification mechanism

  Art. 72 Damage compensation

  Art. 73 National indemnification mechanism

Chapter XII Damage compensation, insurance and national indemnification mechanism

Article 72 Damage compensation

For clinical trials ***other than low-intervention clinical trials***, the sponsor shall ensure that compensation in accordance with the applicable laws on liability of the sponsor and the investigator is provided for any damage suffered by the subject. This damage compensation shall be provided independently of the financial capacity of the sponsor and the investigator.

Article 73 National indemnification mechanism

1. Member States shall provide for a national indemnification mechanism for compensating damage as referred to in Article 72.

2. The sponsor shall be deemed to comply with Article 72 where it makes use of the national indemnification mechanism in the Member State concerned.

3. The use of the national indemnification mechanism shall be free of charge where, for objective reasons, the clinical trial was not intended, at the time of submission of the application for authorisation of that clinical trial, to be used for obtaining a marketing authorisation for a medicinal product.

For all other clinical trials, the use of the national indemnification mechanism may be subject to a fee. Member States shall establish that fee on a not-for-profit basis, taking into account the risk of the clinical trial, the potential damage, and the likelihood of the damage.

Clinical Trial Insurance in UK

- 2012 July, a new draft guidance on clinical trial insurance was introduced in UK to effectively accelerate ethics committees' approval process.
- CROs and their sponsors will be asked to submit a new "more straightforward" document detailing they have the correct insurance for their trial.
- £5m in aggregate for protocol in first-in-human studies, and £2m in aggregate for protocol in Phase I trials.
- This insurance covers participants for injury compensation and legal expenses.
- This document is a much-needed move for the UK, which has been lagging behind many other EU countries which have set legislations in place.

Clinical Trial Insurance in the US

21 CFR 50.25 Elements of informed consent

***(a)Basic elements of informed consent**. In seeking informed consent, the following information shall be provided to each subject:*

(6) For research involving more than minimal risk, an explanation as to whether **any compensation** and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

Clinical Trial Insurance in South Korea
(Doherty 2010)

- Between 2004 and 2009, the number of clinical trials in South Korea increased more than double. Moving the country's ranking from 34th to 12th internationally.*
- The amount of product liability insurance coverage is much lower in South Korea. Generally, the limits for the typical policy purchased in South Korea are usually $100,000-300,000 compared with $2-10 million in the United States.
- The standard policy in South Korea provides coverage for medical expense and indemnity, but does not cover legal liabilities.

Legal Regulation on Insurance & Compensation in Taiwan

- **The Sponsor's Obligation of Applying liability insurance**

  Guideline for Good Clinical Practice－GCP: *Article 47*
  (藥品優良臨床試驗準則第47條)

  the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, **except for claims that arise from malpractice and/or negligence**.試驗委託者應負責試驗主持人或試驗機構因試驗所生之賠償責任或投保責任保險。但因試驗主持人或試驗機構之醫療疏失所致者，不在此限。

Legal Regulation on Insurance & Compensation in Taiwan

- **Medical Care Act: *Article 79***

  The written informed consent should include….

  6. Trial related damage compensation and health insurance mechanism.

  醫療法第79條 醫療機構施行人體試驗時，應善盡醫療上必要之注意，並應先取得接受試 驗者之書面同意....第一項書面，醫療機構應至少載明下列事項，並於接受試驗者或法定代理人同意前，以其可理解方式先行告知：一、試驗目的及方法。 二、可預期風險及副作用。三、預期試驗效果。四、其他可能之治療方式及說明。五、接受試驗者得隨時撤回同意之權利。**六、試驗有關之損害補償或保險機制。**七、受試者個人資料之保密。 八、受試者生物檢體、個人資料或其衍生物之保存與再利用。

Legal Regulation on Insurance & Compensation in Taiwan

- **No Exemption from liability—GCP: Article 18**

  None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

  藥品優良臨床試驗準則第18條

  受試者同意書及提供受試者之任何其他書面資料，不得有任何會造成受試者、法定代理人或有同意權之人放棄其法定權利，或免除試驗主持人、試 驗機構、試驗委託者或其代理商責任之記載。

Liability Insurance Statistic Data in Taiwan 2007-2011

中華民國100年責任保險賠款率統計表
按客戶別、風險類別
（意外事故年度制）

2011 LOSS RATIOS FOR LIABILITY INSURANCE
BY TYPE OF INSURED、SUB-LINE OF BUSINESS
(ACCIDENT-YEAR BASIS)

單位:新臺幣元　　UNIT: N.T. $

客戶別 Type of Insured	風險類別 Sub-Line oF Business	事故年度 Accident Year	保費收入 Written Premiums		滿期保費 Earned Premiums		累計已付賠款 Paid Losses	年末未付賠款 Outstanding Losses Year End	已發生賠款 Incurred Losses		賠款率 Losses Ratios %
			件數 No.	金額 Amount	件數 No.	金額 Amount	金額 Amount	金額 Amount	件數 No.	金額 Amount	
			(1)	(2)	(3)	(4)	(5)	(6	(7)	(8)=(5)+(6)	(9)=(8)/(4)
商業 Commercial	藥物臨床試驗責任保險 The First Human Clinical Trial	2007	85	17,706,249	56	9,599,575	0	0	0	0	0.00
		2008	97	19,109,584	81	14,755,872	0	55,000	2	55,000	0.37
		2009	121	23,120,697	117	21,302,142	0	0	0	0	0.00
		2010	137	24,017,169	114	22,713,092	0	0	0	0	0.00
		2011	155	23,564,635	133	23,134,331	9,735	123	3	9,858	0.04

Loss Ratios for Liability Insurance (2001-2011) Concerning **The First Human Clinical Trial**

Year	Written Premium Amount	No.	Losses Ratios
2001	8,021,281	19	0
2002	8,225,614	12	0
2003	5,869,359	15	0
2004	10,044,860	27	0
2005	4,675,000	24	0
2006	8,605,595	54	44.13%
2007	17,706,249	85	0
2008	19,109,584	97	0.37%
2009	23,120,697	121	0
2010	24,017,169	137	0
2011	23,564,635	155	0.04%

Clinical Trial Insurance in Taiwan

- Clinical Trial Insurance institution started from year 2000.
- There are three authorized underwriters in charge of clinical trial liability insurance:
  1. Fubon Insurance (富邦產物保險)
  2. The First Insurance Co., Ltd. (第一產物保險)
  3. Tokio Marine Newa Insurance Co., Ltd.(新東京海上產物保險)
- Sponsors increasingly take clinical trials liability insurance to cover unexpected injury raised by the trials.
- However, the insurance percentage is still low comparing to the Western countries.
- The maximum compensation is low (2 million NT=66,000 USD)

Summary & Suggestion

- International guidelines require compensation & insurance for clinical trial be specifically addressed in protocol and informed consent before conducting research.
- In general, multinational trials sponsored by big pharmaceutical companies provide more comprehensive insurance & compensation coverage.
- PI initiated studies provide less sufficient insurance & compensation coverage due to lack of funding.
- National regulations play important role in facilitating insurance & compensation mechanism for human subject protection (national indemnification mechanism)

Summary & Suggestion

- The DoH principle: "The protocol should include information regarding …… **provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study."**
- **Says only basic requirement of "compensation" without addressing "insurance"…**
- Consider adding "insurance"? : …"provisions for treating, insurance, and/or compensating subjects

Ali mountain

Shi-tao

Jade Mountain

Sun-moon lake

Taipei 101 tower

National Palace Museum

Chio-fen

Longshan Temple

Thank you for you kind attention!