Safe Drugs Save Lives

Clinical Trials Insurance

Dr. Rachel Kyeyune Bakyayita

Presentation Outline

- Introduction
- Legal and regulatory framework
- Development of the guideline
- Sections of the Guideline
- Risk Assessment Matrix

Introduction

1950's: Thalidomide disaster

- Sleeping pill, presumed safety, over-the-counter access *but* preclinical tests had not looked at drug effects during pregnancy
- Dr. McBride used it "off-label" to alleviate morning sickness
- Over 10,000 children had been affected by the time the link was made between drug & effects
- Long, criminal trial followed which led to both manufacturers and licensing body financially supporting the victims
- More rigorous drug approval & monitoring systems in place today at the US FDA

Introduction

1996: Trovan trial in Nigeria

- Kano was hit by the worst ever meningococcal meningitis epidemic.
- 100 children received a new oral antibiotic by Pfizer-trovafloxacin (Trovan) Vs 100 who received ceftriaxone *but at lower dose*
- 5 died on Trovan Vs 6 on ceftriaxone however consent around the experimental drug was questioned

Introduction

- Many children developed neurological sequelae allegedly due to Trovan
- Over 15 year long criminal battle ensued & Pfizer had to compensate the families

Introduction

2006: TGN1412 and the Elephant men

- Experimental leukemia drug successfully tested in animals and ready for the FIH trial. Trial site was an independent clinic on leased land, North West of London. Manufactured by TeGenero, sponsored by Parexel
- In less than 1 hour of receiving the IMP, 6 volunteers were rushed to ICU: vomiting, pain, tremors, excessive sweating, fever, body swelling, organ failure….*cytokine storm*
- Investigations by the MHRA revealed that the trial protocol had been implemented to the dot *but* the safe dose for humans had not been properly estimated from preclinical data

Introduction

January 2016: BIA 10-2474 Rennes, France

- Phase I Trial was run by a CRO called Biotrial for a Portuguese drug company named Bial Portela
- BIA 10-2474 inhibits an enzyme which had potential implications in treatment of anxiety, chronic pain and neurodegenerative disease.
- BIA 10-2474 was found to have **"off-target"** effects i.e inhibited many other enzymes →not selective
- Multiple groups of volunteers were to be tested for various dosing regimens and food interactions.
- One subject **died,** four others suffered neurological damage.
- Remaining subjects were still dosed the following morning—no provision for revised consent.

Introduction

Two months ago: Northern Uganda

- Notification of a **death** in a child following a trial procedure was submitted to the REC of record with NDA in copy.
- Death occurred before the first dose of the IMP
- Death was deemed ***related to trial procedure*** by both Sponsor and Investigator

Introduction

- Clinical trials are ***not without*** risk
- Risk arises from the **IMP** + **Trial procedures**
- Clinical trials insurance is a mechanism of managing and compensating a human subject due to bodily injury or death as a result of participation in a trial

Introduction

- Clinical Trials Insurance also encompasses provision of indemnity for the investigator/institution
- Need for a ***causal relationship*** between the bodily injury and trial participation
- Clinical Trials Insurance is ***not synonymous*** with national health insurance service

Legal and regulatory framework

World Medical Association **Declaration of Helsinki**: Ethical Principles for Medical Research Involving Human Subjects

General principles:

- Principle #15:

Appropriate compensation & treatment of subjects who are harmed as a result of participating in research *must* be ensured

Legal and regulatory framework

Scientific Requirements & Research protocols

- Principle # 22:

The protocol should contain a statement of ethical considerations & should indicate how the principles in this Declaration have been addressed.

The protocol should include….information regarding provision for treating and/or compensating subjects who are harmed as a consequence of participation in the research study

Legal and regulatory framework

Sections 5.8.1 &5.8.2 of ICH GCP E6 R2

1. 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

2. Sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s)-

Legal and regulatory framework

CIOMS International Ethical Guidelines for Health-related Research Involving Humans, 2016

Guideline #14: Treatment &compensation for research-related harms

- *Sponsors must seek adequate insurance to cover compensation, independent of proof of fault. Arrangements for free treatment and compensation should be described in the protocol and the informed consent*

Legal and regulatory framework

Section 6.5 National Guidelines for Research involving Humans as Research Participants, 2014- (*Under revision)*

The sponsor and researcher shall put in place a mechanism for compensating research related injury at the commencement of a study. The mechanism, which may include, inter alia, insurance and medical care, should be acceptable to the REC

Legal and regulatory framework

National Drug Policy and Authority Act, Chapter 206

- Section 40: *No person may carry out any clinical trial unless he or she is in possession of a certificate*

- Section 5: *Establish and revise professional guidelines and disseminate information to health professionals and the public*

Legal and regulatory framework

Regulations 4, 7, 15 and 20 of the National Drug Policy and Authority (Conduct of Clinical Trials) Regulations, 2014

Sponsor shall provide insurance for the subjects against any clinical trial related injuries or harm, and indemnity for the investigator, against claims arising from the clinical trial, except for claims that arise from malpractice or negligence

Guideline Development

February 2018: Meeting between IRA, NDA, UNCST to discuss development of national policy/guideline on clinical trials insurance and review of draft guideline developed by NDA

July-August 2018: Follow up meetings to refine the draft

Guideline Development

- Document review: Benchmarked guidelines for Malawi, Tanzania
- Meetings with IRA to refine the guideline
- Stakeholder input

Sections of the guideline

- Introduction
- Type and Scope of insurance cover
- Period of insurance coverage &compensation
- Obtaining the no-fault insurance cover
- Authenticity of insurance documents
- Governing policy & Law
- Review of submitted documents
- Policy exclusions

Scope of the guideline

- So far it addresses insurance for trial participants and *not* professional indemnity

- Applies to trials involving investigational medicinal products that require authorization/certificate (refer to NDA guidelines for conduct of clinical trials)

Scope of the guideline (2)

- Trials where the product safety is largely unknown

- Trials proposing changes to an originally approved dosage, route of therapeutic administration, formulation, combination, dosage or usage of an investigational/pharmaceutical product(s)

Period of coverage

- Research-related harm may occur *during* the running period of the trial or *after* the trial is completed thereby necessitating insurance coverage and compensation during and after trial is completed.

- What is the appropriate period of coverage for the Uganda context? Trial-specific context?

Type of insurance coverage

- No-Fault Insurance Cover: “Proof of negligence or other wrongful conduct need not be established.
- However, the causal-connection between the trial and harm/bodily injury/death shall have to be established to trigger the obligation to make compensation payment

- How can this policy be taken out?

✓ Direct issuance of policy by a locally registered firm

✓ Fronting Agreements

How/Where To Obtain Insurance

- Insurance cover must be obtained through a local insurance firm and broker that is registered and operating under law in Uganda
- All copies of insurance policy to be certified by the Insurance Regulatory Authority (IRA)
- IRA to support in verification of authenticity once MoUs are duly signed

Review of documents submitted

- RECs must determine whether there is adequate arrangement for treatment and compensation.

- Insurance policy must not appear to waive off the rights of the research participants (e. g denying a participant compensation as a result of participant's non-adherence to study procedures or as a result of participant's ignorance, illiteracy or lack of understanding etc.)

- Each trial must have its own specific insurance cover for participants in that trial at that site.

- Provision for participants to directly access the insurance benefits as compensation for harm/injury/death that may occur/manifest during the trial period

Risk Assessment Matrix

- Develop in consultation with the Risk Management unit at NDA
- Sponsor to determine the likely risks and impact of the trial (IMP+ Procedures)
- Use a risk assessment matrix to “quantify” the risks identified and inform the insurance premium

Safe Drugs Save Lives

Risk Assessment Matrix

			Potential Consequences				
			L6	L5	L4	L3	L2
			Minor injuries or discomfort. No medical treatment or measureable physical effects.	Injuries or illness requiring medical treatment. Temporary impairment.	Injuries or illness requiring hospital admission.	Injury or illness resulting in permanent impairment.	Fatality
			Not Significant	Minor	Moderate	Major	Severe
Likelihood	Expected to occur regularly under normal circumstances	Almost Certain	Medium	High	Very High	Very High	Very High
	Expected to occur at some time	Likely	Medium	High	High	Very High	Very High
	May occur at some time	Possible	Low	Medium	High	High	Very High
	Not likely to occur in normal circumstances	Unlikely	Low	Low	Medium	Medium	High
	Could happen, but probably never will	Rare	Low	Low	Low	Low	Medium

Roles of various players

- Sponsor: Provides valid clinical trials insurance (and investigator indemnity)
- RECs: Do causal assessment, determine the need to initiate compensation & adequacy of the compensation arrangements
- NDA/IRA/UNCST: Provide relevant guidance and enforce the requirement

...The health of my patient will be my first consideration...

Canada India Argentina
Indonesia Kenya Malawi
South Africa Philippines
Swaziland Switzerland Tanzania
Ukraine Viet Nam Zambia
Zimbabwe Peru
Uganda

Countries that require clinical trials insurance