Incidents happen
which lessons can we learn?

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Incidents happen: lessons to learn?

Content

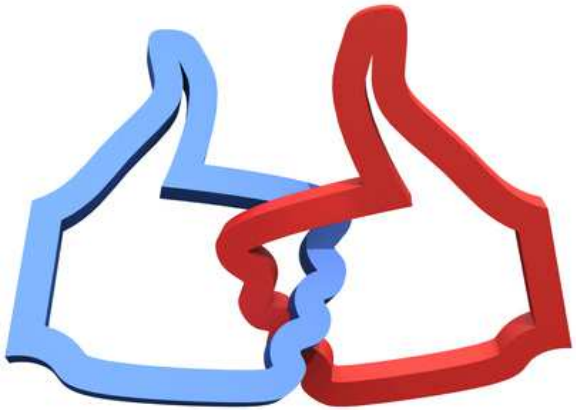
- What is an incident?
- “Incidents” shaping drug regulation & drug development
- Facts and thoughts
- Conclusion

Incidents happen: lessons to learn?

Introduction

Would you consider the following event to be an incident?

- Oil spill



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Incidents happen: lessons to learn?

What is an incident?

Definition: *Oxford dictionary*

-“an instance of something happening; an event or occurrence”

Examples:

- A violent event, such as an assault.
- A hostile clash between forces of rival countries.
- The occurrence of dangerous or exciting things.

Food for thoughts...:

- Positive or negative
- Subjective
- Personal versus society

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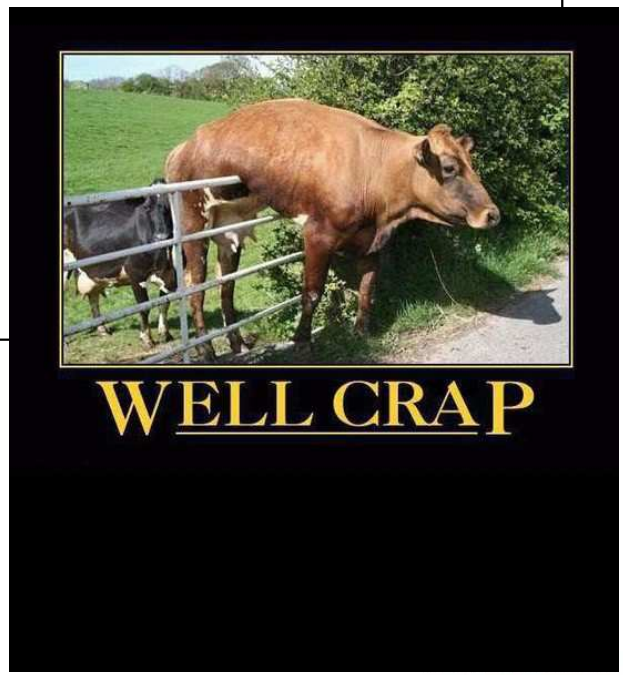
Incidents happen: lessons to learn?

What is an incident?

Definition: *Cambridge dictionary*

- an event that is either unpleasant or unusual
- touching or hitting the surface of something



Incidents happen: lessons to learn?

What is an incident?

Definition: *Merriam Webster dictionary*

- an unexpected and usually unpleasant thing that happens

Synonyms:

- affair
- circumstance
- episode
- happening
- event
- occasion
- occurrence
- thing

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Incidents happen: lessons to learn?

What is an incident?

Incident in drug regulation and drug development:

- an unexpected, unpleasant and rare event
- experienced as unacceptable, to be avoided
- man made problem
- reactions > responses
- risk management: minimisation and mitigation
- How incidents shape drug regulation / development?

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Incidents happen: lessons to learn?

learning from past experiences…

1937 Sulfanilamide elixir incident

- killing over 100 people
- diethylene glycol (DEG) as solvent
- 1938 Food, Drug and Cosmetic Act

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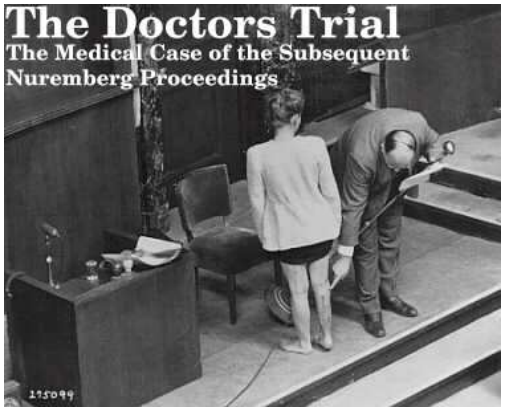
Incidents happen: lessons to learn?

learning from past experiences…

1938 Food, Drug and Cosmetic Act

1947 Nuremberg Code

- post World War II trial of 23 doctors
- unethical experimentation
- Founder Dr. Leo Alexander, April 1947



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Incidents happen: lessons to learn?

learning from past experiences…

- **Ten principles for human experimentation: Voluntary Informed Consent**

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonable to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

Incidents happen: lessons to learn?

learning from past experiences…

- **Ten principles for human experimentation (continued)**

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

Incidents happen: lessons to learn?

learning from past experiences…

- **Ten principles for human experimentation (continued)**

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

- **Basis for current regulations & ethical guidelines of clinical research**

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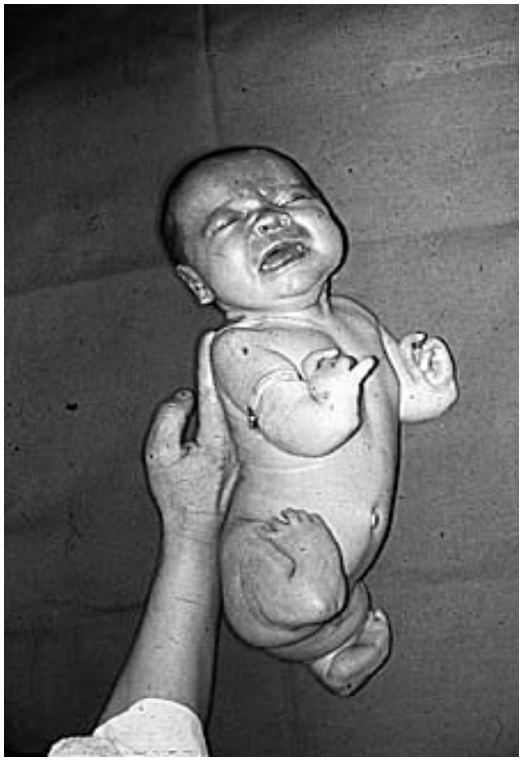
Incidents happen: lessons to learn?

learning from past experiences…

1937 Food, Drug and Cosmetic Act

1947 Nuremberg Code

1961 Thalidomide disaster



- sold since 1956
- 10,000 babies affected
- Drug reaction reporting system

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Incidents happen: lessons to learn?

learning from past experiences…

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1962 Kefhauver-Harris amendment (NDA)

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1964 Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

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learning from past experiences…

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1964 Declaration of Helsinki
1997 ICH-Good Clinical Practice guidelines (GCP)

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1964 Declaration of Helsinki
1997 ICH-Good Clinical Practice guidelines
2001 European Clinical Trial Directive

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

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

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Incidents happen: lessons to learn?

learning from past experiences…

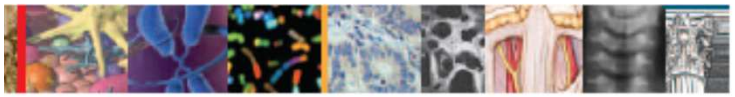

DRUGS TRIAL GUINEA

Writhing, vomiti

they screamed th

FIGHT TO SAVE RYAN AND 'ELEPHANT MAN'

'Dog given drug died'


D JOURNAL of MEDICINE

Volunteers —

rch Nightmare

et Darbyshire, M.B., Ch.B.

Monday, March 13, 2006, eight

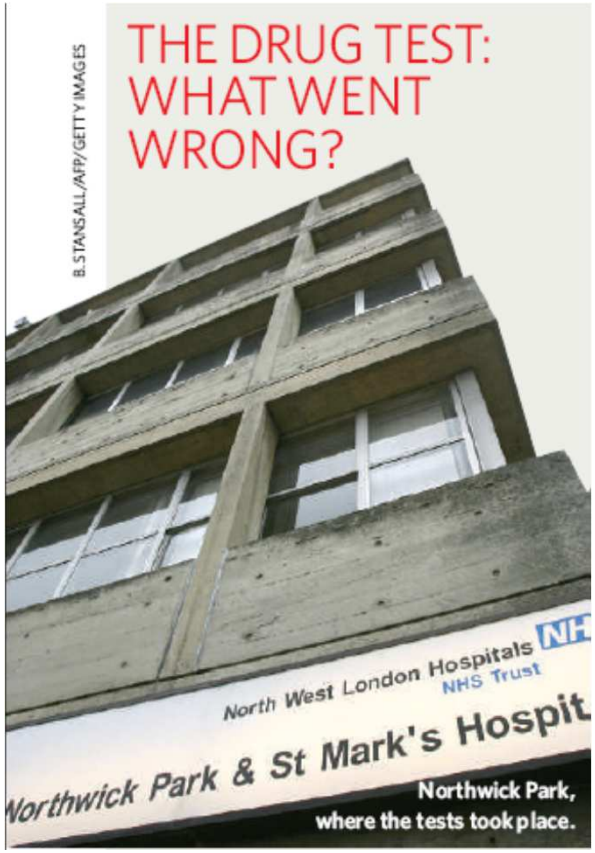
g men entered a trial of a drug

nt by the small German immuno-

pany TeGenero. Six of the volun-

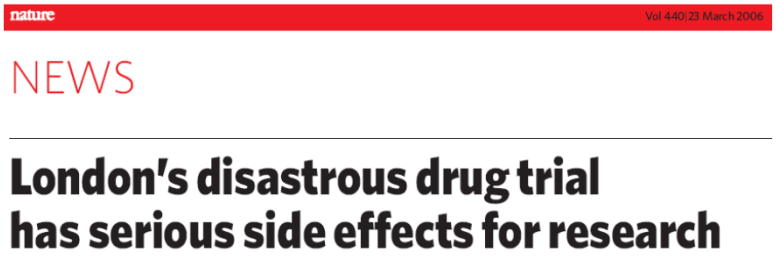
Incidents happen: lessons to learn?

learning from past experiences…



Nature 2006; 440: 388-389

- 19 July 2007: EMEA guideline on First-in-Human clinical trials
- August 2007: ABPI guidelines for phase I clinical trials
- 28 August 2007: MHRA proposal for a voluntary accreditation scheme for phase I clinical trial units in the UK



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1964 Declaration of Helsinki
1997 ICH-Good Clinical Practice guidelines
2001 European Clinical Trial Directive
2007 EMA guideline on First-in-Human clinical trials

MABEL

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1997 ICH-Good Clinical Practice guidelines
2001 European Clinical Trial Directive
2007 EMA guideline on First-in-Human clinical trials
2014 European Regulation

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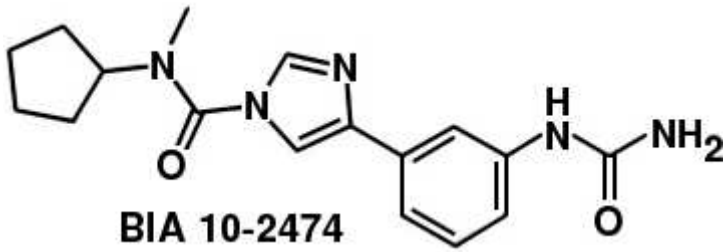
Incidents happen: lessons to learn?

Shaping the future: BIAL 10-2474

First-in-Human Clinical Trials — What We Can Learn from Tragic Failures

Sergio Bonini, M.D., and Guido Rasi, M.D.

On January 10, 2016, a healthy volunteer who had received 50 mg per day of a fatty acid amide hydrolase (FAAH) inhibitor for 5 days as part of a first-in-human phase 1 clinical trial was admitted to Rennes University Hospital with neurologic and gait disturbances. After a dramatic worsening of neurologic symptoms, the participant died on January 17.



BIA 10-2474

N Engl J Med 2016; 375: 1717-1725

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Incidents happen: lessons to learn?

Shaping the future…

SERIOUS ADVERSE EVENTS IN PHASE I
FRENCH CLUB PHASE I REGISTER 2004-2010

POPULATION

Healthy subjects	All (100%)	Young		Elderly	
		Male	Female	Male	Female
Total	43462	70.7%	23.7%	2.7%	2.8%

SAE INCIDENCE

SAE	Total number and incidence (%)		Related (number, %, incidence)			Unrelated (number, %, incidence)		
Total	179	$4^0/_{00}$	63	35%	$1.4^0/_{00}$	116	65%	$2.6^0/_{00}$

Alain Patat, BAPU meeting Dec 2016

Incidents happen: lessons to learn?

Shaping the future…

BAPU survey on SAEs: period 2009 - 2015

	All	Young (<65 y)		Elderly	
		Male	Female	Male	Female
Total	21,147				
Healthy subjects	19,740 (93%)	14,041 (71.1%)	4,807 (24.4%)	474 (2.5%)	418 (2.1%)
Patients*	1,407 (7%)				

**Special populations*

Incidents happen: lessons to learn?

Shaping the future…

BAPU survey on SAEs: period 2009 - 2015

	Total #, incidence		Related (#, %, incidence)			Unrelated (#, %, incidence)		
SAE* SUSAR	91	4.3 ‰	8	9%	0.38 ‰	82	91%	3.9 ‰

** At a total of 21,147 participants*

Incidents happen: lessons to learn?

Shaping the future…

Over the past 50 years:

- Worldwide: 12 deaths reported in phase 1 clinical trials
  - 5 possibly drug related
  - Underreporting…
- 50,000 to 100,000 subjects dosed / year
  - 2,5 to 5 million subjects over 50 years
- Risk of death is 1 in 500,000 subjects

(Alain Patat, BAPU meeting Dec 2016)

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Incidents happen: lessons to learn?

Shaping the future…

Over the past 50 years:

- Small number of drug related SAEs: 1 per 1000
- Small number of drug reated fatalities: 1 per 500,000
- What is small? What is acceptable …
  - Risk comparable to bungee jumping
  - Safer than: American football, scuba diving, sky diving, …
  - …

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Incidents happen: lessons to learn?

Shaping the future…

What is acceptable?

- "*Zero risk does not exist*", however…
- It can be prevented:

  "*If you don't dose healthy subjects, they will not experience a drug related SAE…*"
- Is phase 1 research on healthy subjects a necessary evil?

> Clinical trials of an IMP that do not benefit subjects - whether they be healthy subjects or patients - are called phase 1 or non-therapeutic trials.[7]

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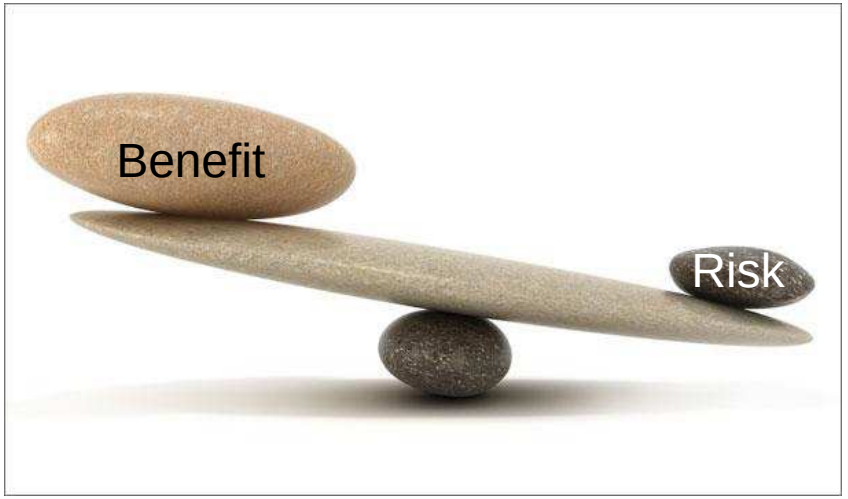
Incidents happen: lessons to learn?

Shaping the future…

TO THE EDITOR: Kerbrat et al. and Bonini and Rasi describe a phase 1 study that underwent review by an institutional review board. Nevertheless, I question whether it is ethical to enroll healthy persons in phase 1 (toxicity) trials.

According to the principle described in the Belmont Report,[1] beneficence implies a reasonable risk-to-benefit ratio. For a healthy volunteer enrolling in a toxicity trial, there is clearly risk but no medical benefit. Monetary compensation or appeals to altruism in the name of humankind are only avenues for ethical abuse. The only cohort that can be considered to derive at least a modicum of medical benefit from volunteering in a phase 1 trial consists of patients who have the condition for which the drug is being developed as a treatment. They should be the only persons who are asked to volunteer for a phase 1 trial.

Irwin Nash, M.D.
Yale School of Medicine
New Haven, CT



N Engl J Med 2017; 376: 393

Incidents happen: lessons to learn?

Shaping the future…

How to minimize the risks? Investigators and industry

- Competence and experience needed
  - Training…
- Transparency
- Not necessarily *more* information needed, but *better* communication
- Independent expert data review?

Incidents happen: lessons to learn?

Shaping the future…

How to minimize the risks? Competent authorities

- Revise existing guidelines and rules
- Develop strategies to make drug development safer
  - Prevent over-volunteering…
- Does this call for more control by CA?
  - Inspections
  - Accreditations

Incidents happen: lessons to learn?

Conclusion…

First-in-Human Clinical Trials — What We Can Learn from Tragic Failures

Clinical trials are still the best tool for providing the evidence needed for drug approval and appropriate clinical practice. Phase 1 trials are generally safe; there have been only two trials with very severe adverse events affecting several volunteers among the 14,700 studies (3100 first-in-human studies) involving 305,000 participants that have been conducted in the EU since 2005. It is hoped that the revised EMA guidelines, when available, will enhance strategies to identify and minimize risks for trial participants and to ensure that first-in-human trials throughout the EU member states are conducted in a safe, efficient, transparent, and harmonized manner for the benefit of human health.

N Engl J Med 2016; 375: 1788-1789

Incidents happen: lessons to learn?

Conclusion…

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