

Is Phase I safe ?

Michel SIBILLE

and

French Club Phase I

Safe ?

- YES... based on the available data
- BUT... there are risks:
 1. Non accurate methods or non compliance
 2. New risks for future
- AND... two questions

The available data

Safety in Phase I and
Experimental research

Levinski NG NEJM 2002, 347: 759

« I was unable to identify a comprehensive list of deaths of normal volunteers in the United States... »

Questions:

- Number of volunteers ?
- Number of deaths & serious adverse events ?

Number of healthy volunteers

Phase I and Experimental Research

- *US*: NIH alone, 5510 HV *Lemonick TIME 22.4.2002.*
- *France*: 2002-4, # 6-10000 *Club Phase I register-AFSSAPS*
- *UK*: 92-2001, # 9-10000 *AICRC register*

→ *Worldwide grand total \geq 100000 per year*

Last 30 years	N of subj	Phase I	Experimental research	Reference		
Cardon 1976	934000	+	+	NEJM 1976, 295: 650		
Zarafonetis 1978	29162	+	+	CPT 1978, 24: 127		
Royle 1986	27424	+	+	Br J Clin Pharm, 86, 21: 548		
Orme 1989	8163	+	+	Br J Clin Pharm, 89, 27: 125		
Rosenzweig 1993	1228	+		CPT 1993, 54: 578		
Huic 1996	885	+		Therapie, 1996, 51: 410		
Herman 1997	440	+		Eur J Clin Pharm, 1997, 53: 207		
Sibille 1992-98-03	1901	+		Eur J Clin Pharm, 1992, 42: 389 Eur J Clin Pharm, 1998, 54: 13		
UK AICRC 1992-2001	92510	+		-		
Club Phase I 2004	5523	+		-		

Last 30 years	N of subj	Phase I	Exper research	Serious Adverse events	Per thousand
Cardon 1976	934000	+	+	38	0,04
Zarafonetis 1978	29162	+	+	65	2,2
Royle 1986	27424	+	+	13	0,5
Orme 1989	8163	+	+	48	5,5
Rosen 1993	1228	+		0	
Huic 1996	885	+		0	
Herman 1997	440	+		0	
Sibille 1992-98-03	1901	+		8	3
UK AICRC 1992-2001	92510	+		209	2,2
Club Phase I 2004	5523	+		25	4

Serious Adverse Events

France: Club Phase I register

Whole year survey on 2004

Number of subjects: 5523

Serious AEs: 25 (4 ‰)

- No life threatening, no disability

- Related to tested drug : 9

 - Non related to tested drug : 16

Last 30 years	N of subj	Phase I	Exp. Res.	Deaths
Zarafonetis	29162	+	+	1
Royle	27424	+	+	1
Sibille	1901	+		3
UK AICRC	92510	+		3
Club Phase I + Personal Update	5523	+	+	1 5

Total = 14

Deaths in Phase I and experimental research

N°	Year	Country	Phase I	Exp. Research	Reference
1	1980	US	X		Hastings - Center, 1980, 10:5
2	1985	Ireland	X		Lancet, 1985, I:93
3	1985	UK	X		BMJ, 1985, 290:1359
4	1999	US	X		No publication
5	2004	US	X		Indianapolis Star, 10 Feb. 2004
6	1992-2001	UK	X		AICRC Survey
7	1992-2001	UK	X		AICRC Survey
8	1992-2001	UK	X		AICRC Survey
9	1978	US		X	CPT, 1978, 24:127
10	1996	US		X	NY State Dpt of Health - 96 Press release
11	2000	Australia		X	Med. J. Aust, 1998, 168 (9):449
12	2001	US		X	Science, 2001, 293, 5532:1013
13	2002	US		X	Arterioscler. Thromb. Vasc. Biol. 2002, 22:1046
14	2004	France		X	Club Phase I French register

1. Supposedly healthy, but anorexia nervosa with severe potassium depletion; Interaction with tested drug
Treatment: **lithium and methyl paratyrosine**
2. Supposedly healthy, but psychotic who received the day before a depot I.M. injection of flupenthixol
Treatment: **antiarrhythmic**, death by probable drug interaction.

3. Aplastic anemia (8 months after study)

Treatment: **midazolam**

4. Anaphylactic shock or arrhythmia and inaccurate resuscitation; patient volunteer with mild renal insufficiency

Treatment: **Antibiotic by iv route**

5. Suicide: hanged herself in the Clinical Research Lab.

Treatment: **duloxetine**

6. Unknown cause; **placebo**, one day after study inhouse period
7. Cardiac arrest, predosing period
8. Car accident, one week after study
9. Cerebrovascular haemorrhage, **placebo**

10. Rochester case: **Overdose of lidocaine**-
local anaesthetic used in bronchial fibroscopy

11. Australian case; **Overdose of lignocaine**-
local anaesthetic used in bronchial fibroscopy

12. The Johns Hopkins' case: cough then
respiratory breakdown
Treatment: **inhaled hexamethonium**
(unauthorized drug)

13. Cleveland case: Severe vomiting, hypertension, confusion, acute aspiration pneumonia

Methionine overdose (# 10 fold, proven by PK data).

Subject already participant in another 'WACS' study using vitamin C and betacarotene.

14. Lung cancer, study on biomarker

Analyse causes...

... suggest safety rules

N°	Last 30 years: 14 identified cases of Deaths in Healthy Volunteers	Study and/or drug	Hazard or accident
	<u>PHASE I STUDIES</u>		
1	Supposedly healthy, but anorexia nervosa with severe potassium depletion; Source of interaction with tested drug : Treatment: lithium and methyl paratyrosine.	X	
2	Supposedly healthy, but psychotic who received the day before a depot I.M. injection of flupenthixol; Source of drug / drug interaction to tested drug; Treatment: antiarrhythmic , death by probable drug interaction.	X	
3	Aplastic anemia (8 months after study); Treatment: midazolam.	X	
4	Anaphylactic shock or arrhythmia and inaccurate resuscitation; patient volunteer with mild renal insufficiency; Treatment: Antibiotic by iv route	X	
5	Suicide: hanged herself in the Clinical Research Lab. Treatment: duloxetine	X	
6	Unknown cause (Alcohol ?); placebo, one day after study in housed period		X
7	Cardiac arrest, predosing period		X
8	Car accident; one week after study		X
	<u>EXPERIMENTAL RESEARCH:</u>		
9	Cerebrovascular haemorrhage; placebo treatment		X
10	Rochester case: Overdose of lidocaine -local anaesthetic bronchial fibroscopy	X	
11	Australian case; overdose of lignocaine -local anaesthetic bronchial fibroscopy	X	
12	The Johns Hopkins' case: cough then respiratory breakdown; Treatment: inhaled hexamethonium (unauthorized drug);	X	
13	Cleveland case: Severe vomiting, hypertension, confusion, acute aspiration pneumonia related to methionine overdose (# 10 fold, proven by PK data). Subject already participant in another study 'WACS' using vitamin C and betacarotene.	X	
14	Lung cancer; study on biomarker	X	
17		10	4

The Causes & *the safety rules*

10 non accidental deaths

A/ Screening default : 3 (psychiatric abn. 2)

1. *Qualified process and staff*
2. *Special scrutiny on volunteers already known by team (4/10 deaths)*
3. *Use of REMEDI to detect previous drug consumption (Rapid Emergency Drug Identification Ann. Biol. Clin. 1993, 51, 611)*

The Causes & *the safety rules*

10 non accidental deaths

B/ Study conduct default 7/10

- *Continuous presence of a qualified physician in CPU*
- *Conservative safety rules regarding :*
 - *Drug use*
 - *Procedure implementation*
 - *Unexpected and /or severe AE*

The Causes & *the safety rules*

10 non accidental deaths

DRUGS 7/10

- Parallel drugs: 4
- Overdose: 3 (local anaesthetics (2) and additive (1))
- Non authorized drug: 1

Suggested preventive action:

Special scrutiny ...

Special scrutiny

Donna Shalala NEJM, 2000, 343: 808

1. Non authorized substance
2. Non tested (parallel) drug required for specific studies
ie local anaesthetic....

at least same requirements as for the tested drug:

- Extensive literature review: describe risks
- Rules & limitations for use, in the protocol

The Causes & *the safety rules* Population

A/ Elderly: 5/14 or 3/10 non accidental

Well known increase of disease risk in parallel to age
& also decrease of resistance capacity

Suggested preventive action:

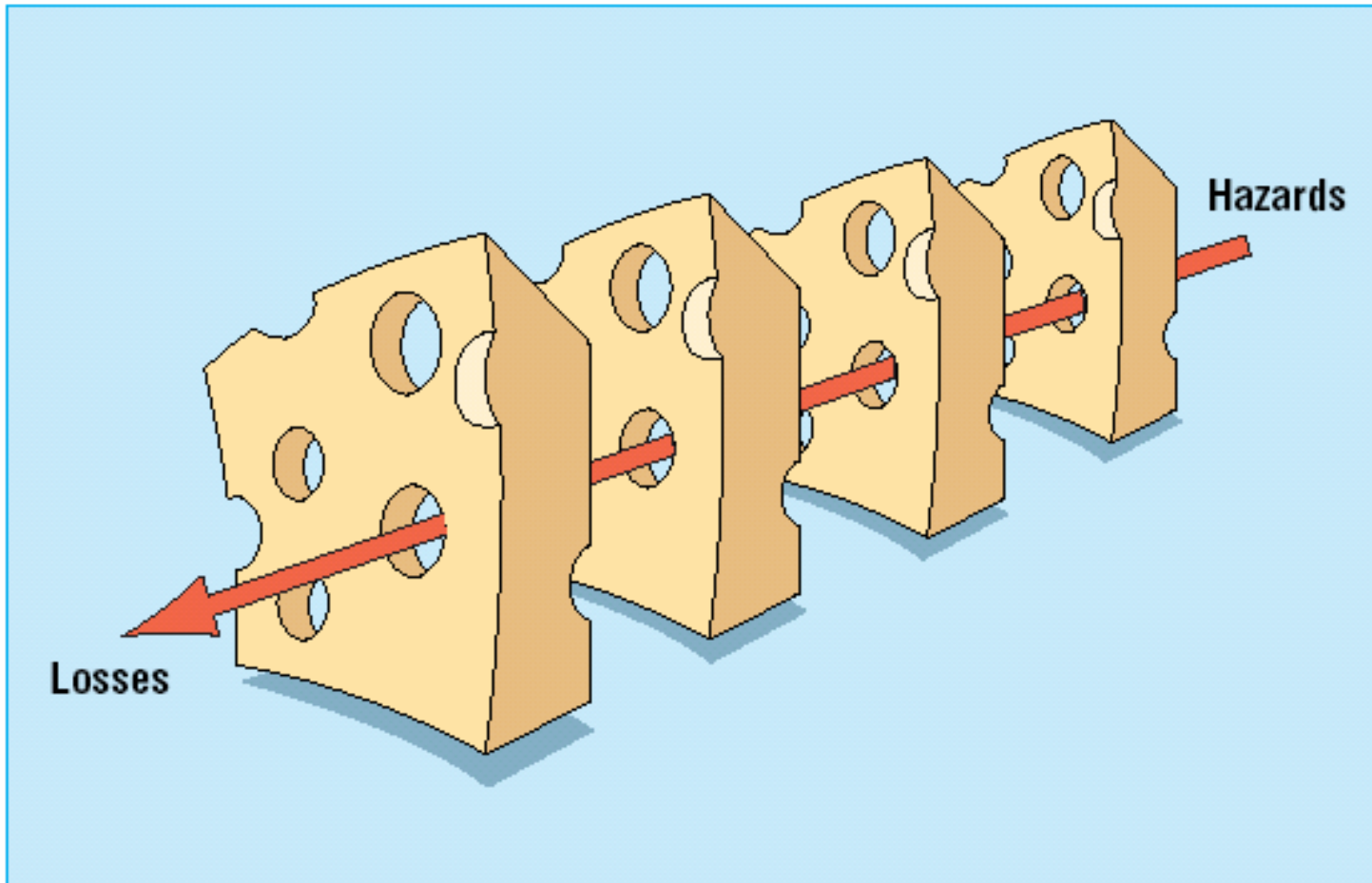
- *More comprehensive screening process in elderly.*
- *Limitation on non benefit studies in healthy elderly
& conservative approach if MTD required in
elderly*

The Causes & *the safety rules* Population

B/ Women: 7/10 non accidental deaths

Why ?

- *Inclusion of women in first-in-man ?*
- *Special scrutiny on protocols in women to make continuous risk assessment*



The Swiss cheese model of how defences, barriers, and safeguards may be penetrated by an accident trajectory

The causes & potential factors

10 DEATHS RELATED TO STUDY AND / OR DRUG								
N°	Screening	Subject working with or known by study staff	Study conduct	Drug overdose	Unauthorized drug	Elderly	Woman	Number of
1	X	X	X				X	4
2	X	X						2
3								.
4			X			X		2
5			X				X	2
10			X	X			X	3
11		X	X	X			X	4
12		X	X		X		X	4
13			X	X			X	4
14	X						X	3
Total	3	4	7	3	1	1	7	

10 DEATHS RELATED TO STUDY AND / OR DRUG

N°	Screening	Subject working with or known by study staff	Study conduct	Drug overdose	Unauthorized drug	Elderly	Woman	Preventable	
								Yes	No
1	X	X	X				X		
2	X	X					X		
3								X	
4			X			X	X		
5			X				X		
10			X	X			X		
11		X	X	X			X		
12		X	X		X		X		
13			X	X		X	X		
14	X					X	X		
Total	3	4	7	3	1	1	7	9/10	1

First Conclusion

- Is Phase I safe ?
 - YES ... only 10 non accidental deaths / 30 years & > 100,000 volunteers per year
 - YES ... **only ONE non preventable death**
 - YES... IF ... safety rules are accurate & respected

Safe ?

- YES... based on the available data
- BUT... there are risks:
 1. Non accurate methods or non compliance
 2. New risks for future
 - Experimental medicine
 - Conflict-of-interest
- AND... two questions

Future of Clin Pharm is Experimental medicine

IN DRUG RESEARCH, THE GUINEA PIGS OF CHOICE ARE, WELL, HUMAN.

« Researchers repeated the experiment 70 times: a healthy volunteer would receive a chemical injection, then be left alone to ride out an artificially induced panic attack.... Each volunteer was put through the same test a few days later, but this time most of them first received an experimental antianxiety drug... »

The New York Times Aug.4, 2004 by Andrew Pollack

Special scrutiny

- Criterion 1: **Initial translation** of scientific advances into humans
- Criterion 2: **Risk** for significant harm and no potential for direct medical benefit
- Criterion 3: Ethical questions about research for which there is **no authoritative consensus**

Carol LEVINE Ann Intern Med 2004,140:220

Conflict-of-interest

Do exist ! Not avoidable !

Could be financial & direct but also indirect – research activities or publishing activities

- USA, from 80 to 2000, industry's share in biomedical research increases **from 32% to 62%**
- Phase I, by nature, is sponsored by industry

Best proposals

- Fully **disclose** nature and extent of relationships
- **Publish** all results

JE Bekelman,

JAMA, 2003, 289:454

EA Boyd

Acad Med 2003,78:769

NG Levinski

NEJM 2002,347:759

Safe ?

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- BUT... there are risks:
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- **AND... two questions**

Repeat participation among healthy research volunteers

- Only one at a time
- Exclusion period after a research study participation
- Limitation in the total amount of money to avoid « professionalism »
 - Follow-up after study
 - Volunteer registry

French Law

Carl LTishler

Volunteer National file

Perspec. Biol. Med. 2003, 46, 508

Long term follow-up & volunteer register

Feasibility ?

Restricted to

- Repeat participation
- Multiple dose protocols
- Probability of risks
ie Psychotropic drugs
Immune system activity

Levinski NG NEJM 2002, 347: 759

« *I was unable to identify a comprehensive list of deaths of normal volunteers in the United States.*

The FDA requires reports of deaths during clinical trials of investigational drugs, but the information is not made public. »

Last risk: **holding back information**

Ex: A new drug in a new class with big unexpected new risk → mandatory reporting from investigator → sponsor → agencies

But: * no publication by investigator
* holding back information by sponsor & agencies

Thus: * scientific handicap
* **risk on second drug in class**
* ethically questionable custom

Make available the research results
Bekelman JAMA 2003,289,454

« *All investigators and sponsors undertaking human participants research should ...make available all research results from completed trials in a comprehensive, publicly accessible registry* »

Rennie *Fair conduct and fair reporting trial*
JAMA 1999,282:1766

Horton *Time to register randomised trials*
Lancet 1999, 354: 1138

Mc Cray *Better access to information about clinical trials*
Ann Med Intern 2000, 133:609

Conclusions and/or recommendations

1. Safe...yes, if safety rules respected
2. Special scrutiny on emergent risks:
experimental medicine including
« parallel drugs » used for
pharmacodynamics or risky procedure
3. Long term follow-up in restricted
conditions

.../...

4. Share experience and knowledge

Proposal for Phase I & Experimental Research

Per country or **Europe**,

- Create **a register** on Deaths & Serious AEs
(life threatening, disability ...)
- Independent organism or **Health authorities**
- Give access to such register*

* Take care of confidentiality

HEALTHY VOLUNTEERS

Club Phase I register France - 2004

	Men	Women	
Young	4312	783	
Elderly	169	259	
Total	4481	1042	5523

Serious AEs

Club Phase I register France 2004

	Men		Women		
	Young	Elderly	Young	Elderly	
Related	5	-	-	4	9
Non related	9	2	1	4	16
	14	2	1	8	25