PRIORITIZATION OF CLINICAL RESEARCH

SILVIO GARATTINI

MARIO NEGRI
ISTITUTO DI RICERCHE
FARMACOLOGICHE

Milan 30th November 2007

PERSPECTIVE

KNOWLEDGE

INDUSTRY

NHS

PATIENTS

FEASIBILITY

STATE OF THE ART

INFRASTRUCTURE

TEAMS

INPUT

INSTITUTIONS

SCIENTIFIC SOCIETIES

PATIENT ASSOCIATIONS

CONSUMER SOCIETIES

INDIVIDUALS

AUDITING

DOCUMENTS

WEBSITE

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

CLINICAL TRIALS IN ITALY (2000-2006)

PHASE	ALL	ONCOLOGY	CARDIOVASCULAR
2	1.515 (35.0)	743 (62.2)	98 (20.7)
3	2.262 (52.3)	421 (35.3)	303 (63.9)
4	384 (8.9)	27 (2.3)	63 (13.3)
TOTAL	4.323 (100%)	1.194 (100%)	474 (100%)

SOURCE: OsSC 2007

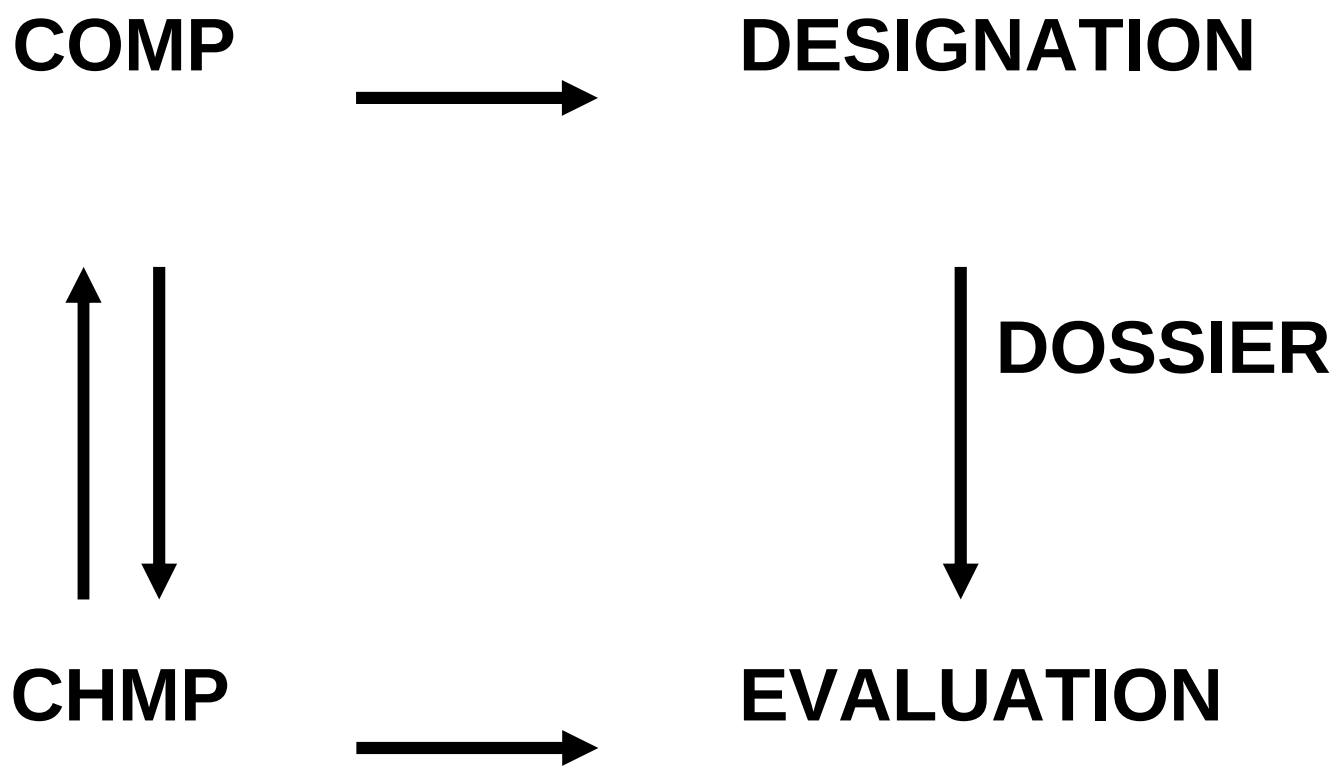
OVER 80% OF THESE TRIALS ARE SUPPORTED AND EXECUTED BY PHARMACEUTICAL COMPANIES

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs


COMP
DESIGNATION
DOSSIER
CHMP
EVALUATION

ORPHAN DRUG PROGRAM

	USA	JAPAN	EUROPE
BEGINNING	1987	1993	1999
PATIENTS	< 220.000	< 50.000	< 200.000
EXCLUSIVITY	10 yrs	10 yrs	10 yrs
GRANTS	yes	yes	no
DETAXATION	yes	yes	no
AGENCY	FDA	PMDA	EMEA

MAJOR PROBLEMS IN THE APPROVAL OF ORPHAN DRUGS

LACK OF DOSE FINDING

LACK OF PHASE 3 TRIALS

SURROGATE END-POINTS

SHORT DURATION OF TREATMENT

SMALL NUMBER OF PATIENTS

POOR KNOWLEDGE OF ADVERSE REACTIONS

PATIENTS WITH RARE DISEASES SHOULD NOT BE PENALIZED.

THEY HAVE THE RIGHT TO HAVE DRUGS PROVIDED WITH QUALITY, EFFICACY AND SAFETY AS ALL THE OTHER PATIENTS AFFECTED BY MORE COMMON DISEASES

ORPHAN DRUGS

DESIGNATED 479

APPROVED 041

FOR 6.000 RARE DISEASES

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs

- Sub populations excluded by clinical trials

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

A Systematic Sampling Review

Harriette G. C. Van Spall, MD
Andrew Toren, MD
Alex Kiss, PhD
Robert A. Fowler, MD, MS

Conclusions The RCTs published in major medical journals do not always clearly report exclusion criteria. Women, children, the elderly, and those with common medical conditions are frequently excluded from RCTs. Trials with multiple centers and those involving drug interventions are most likely to have extensive exclusions. Such exclusions may impair the generalizability of RCT results. These findings highlight a need for careful consideration and transparent reporting and justification of exclusion criteria in clinical trials.

JAMA. 2007;297:1233-1240

OUT OF 9664 SUBJECTS ENROLLED IN TRIALS STUDYING OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

ONLY 207 PATIENTS $\geq$ 65 YEARS (2.1 %)

214 PATIENTS 75-84 YEARS

0 PATIENTS $\geq$ 85 YEARS

ROCHON et al., 1993

ABOUT 50% OF PEDIATRIC DRUGS
HAVE NEVER BEEN TESTED IN CHILDREN.
DOSES ARE USUALLY EXTRAPOLATED ON
THE BASIS OF mg/Kg BODY WEIGHT

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs

- Sub populations excluded by clinical trials

- Diseases of developing countries

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs

- Sub populations excluded by clinical trials

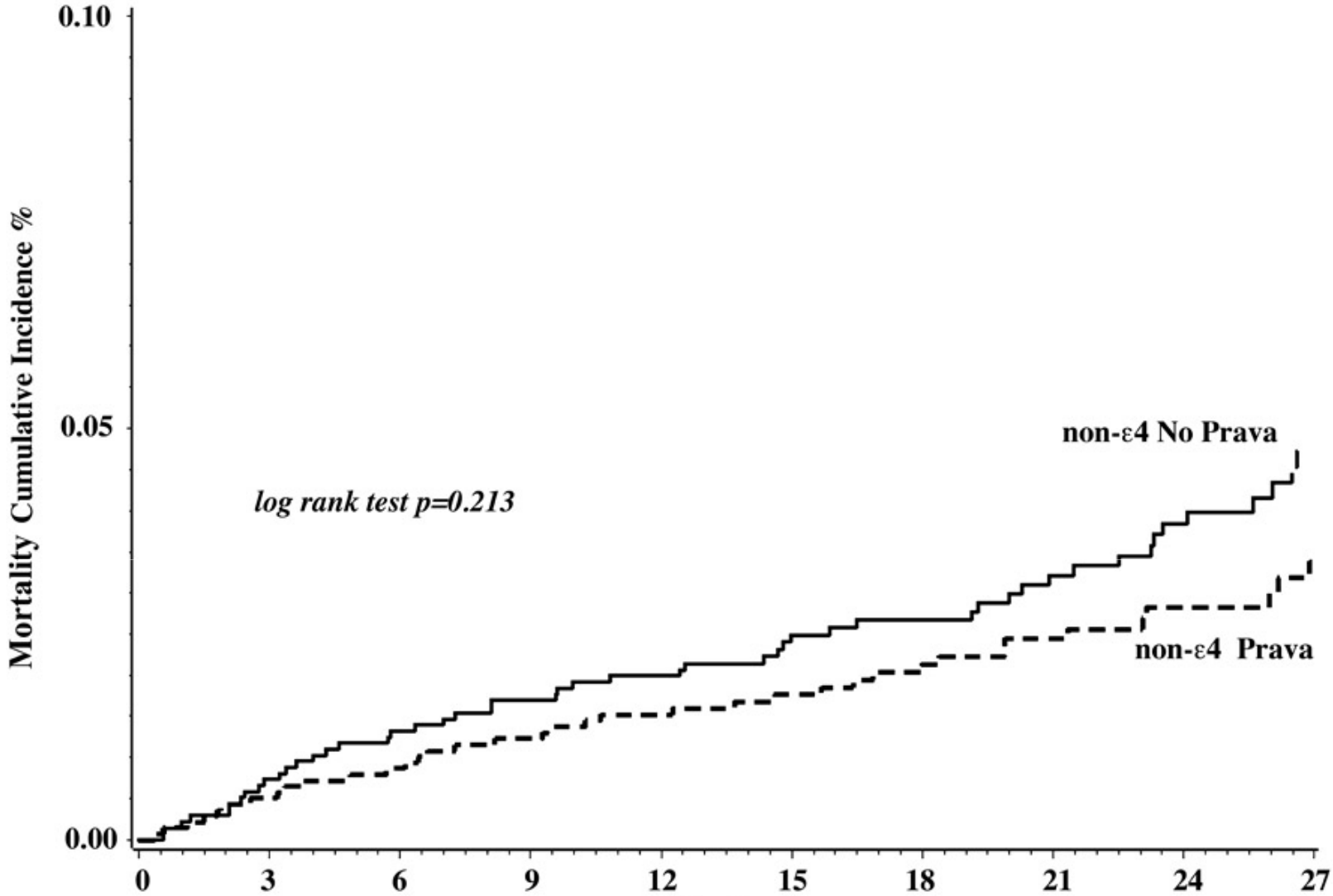
- Diseases of developing countries

- Studies to decrease the NNT

Apolipoprotein E Polymorphisms influence Effect of Pravastatin on Survival after Myocardial Infarction in a Mediterranean Population: the GISSI-Prevenzione Study

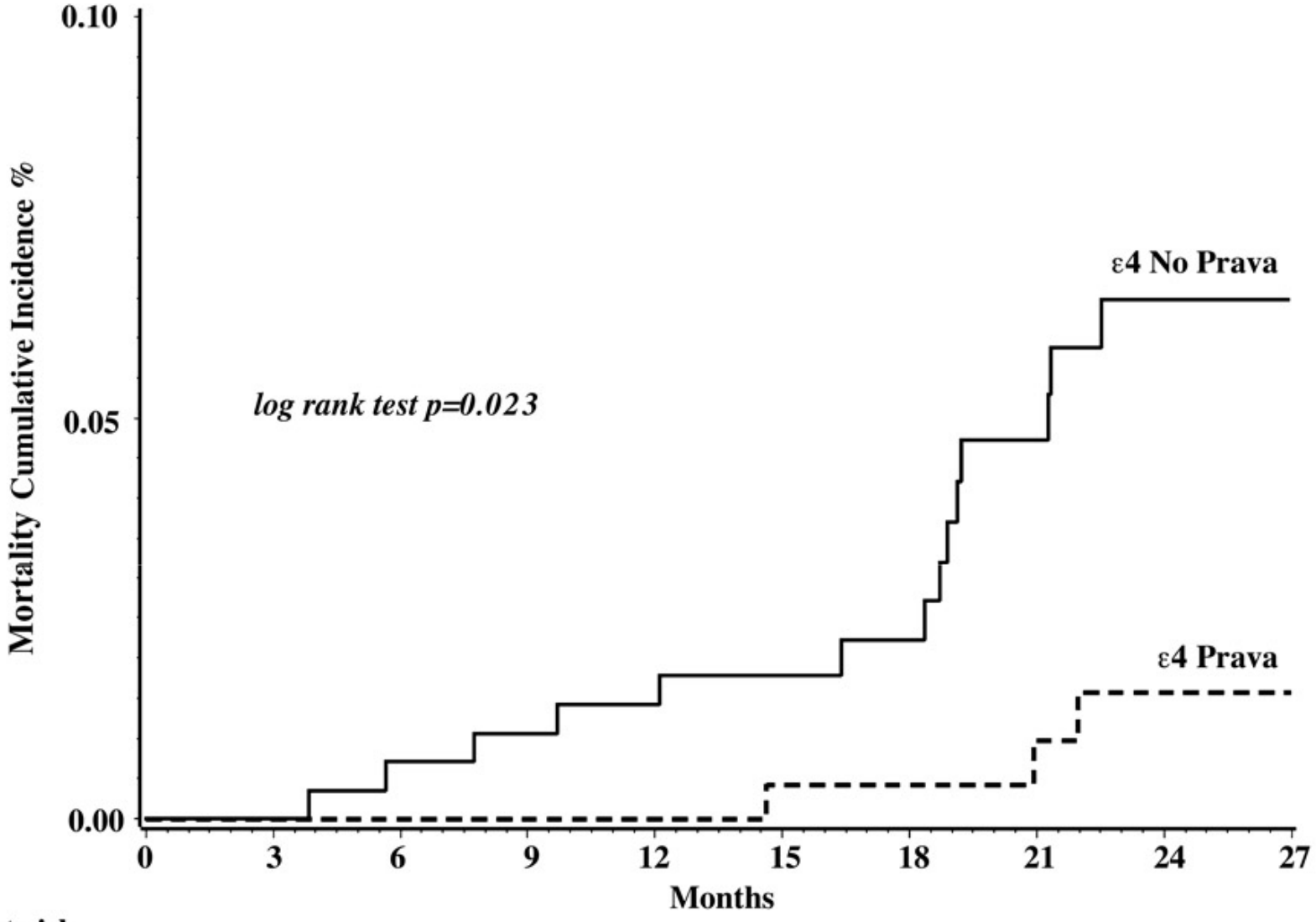
Benedetta D. Chiodini, Maria Grazia Franzosi, Simona Barlera, Stefano Signorini, Cathryn M. Lewis, Andria D'Orazio, Paolo Mocarelli, Enrico Nicolis, Roberto Marchioli, Gianni Tognoni, on behalf of GISSI-Investigators and SIBioC-GISSI Prevenzione Group.

Eur Heart J. in press



N° at risk				
Prava	1387	1358	993	472
No Prava	1363	1330	995	477

Chiodini et al., 2007



N° at risk				
Prava	270	270	202	97
No Prava	284	276	201	85

Chiodini et al., 2007

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs

- Sub populations excluded by clinical trials

- Diseases of developing countries

- Studies to decrease the NNT

- Generics

GENERIC MEDICINAL PRODUCTS ARE USUALLY NEGLECTED BY RESEARCH.

ACE-I vs SARTANS

RANITIDINE vs PPI

THE DANGER IS THE UNDER PRESCRIPTION OF VALUABLE MEDICINES

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs

- Sub populations excluded by clinical trials

- Diseases of developing countries

- Studies to decrease the NNT

- Generics

Head to head comparisons

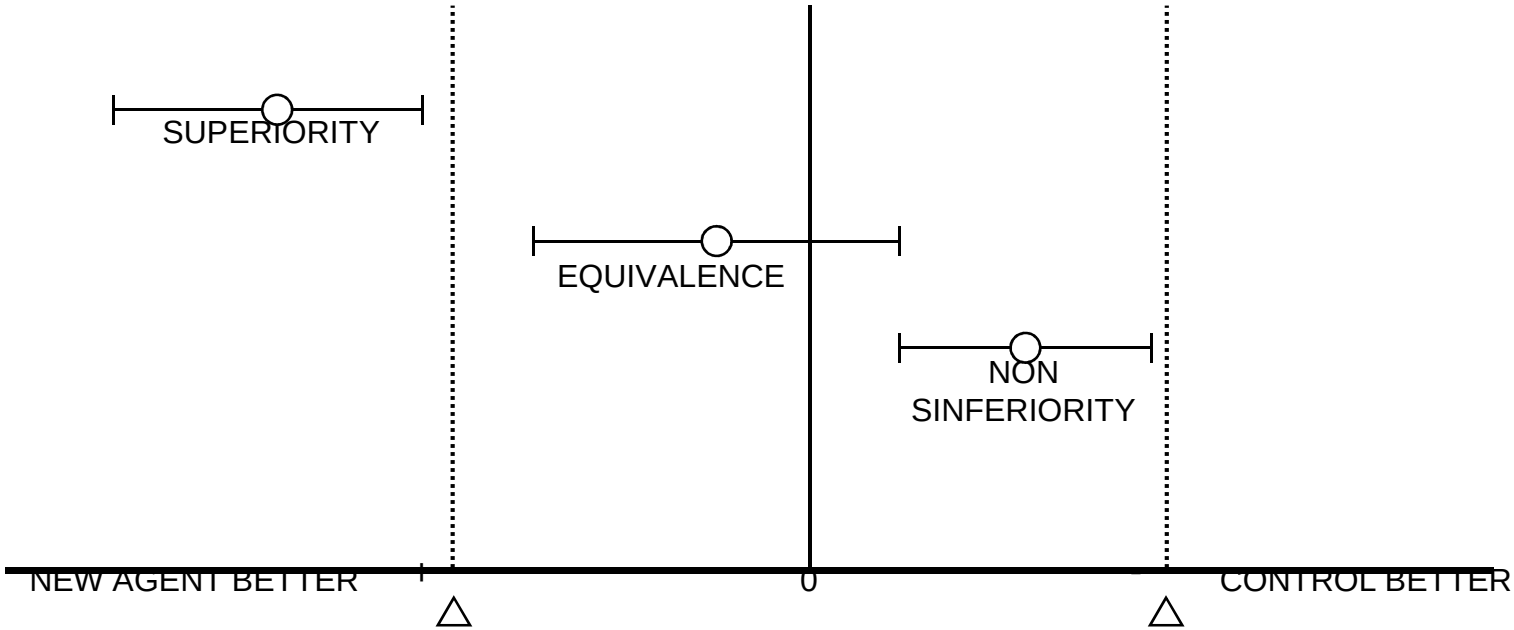
- Single drugs and therapeutic strategies

CLINICAL TRIALS MAY BE DESIGNED TO DEMONSTRATE

SUPERIORITY

EQUIVALENCE

NON INFERIORITY


SUPERIORITY
EQUIVALENCE
NON
SINFERIORITY
NEW AGENT BETTER
0
CONTROL BETTER

18 ANTICANCER AGENTS

21 INDICATIONS

12 ONLY PHASE II

9 PHASE III

6 EQUIVALENCE OR NON INFERIORITY

3 SUPERIORITY

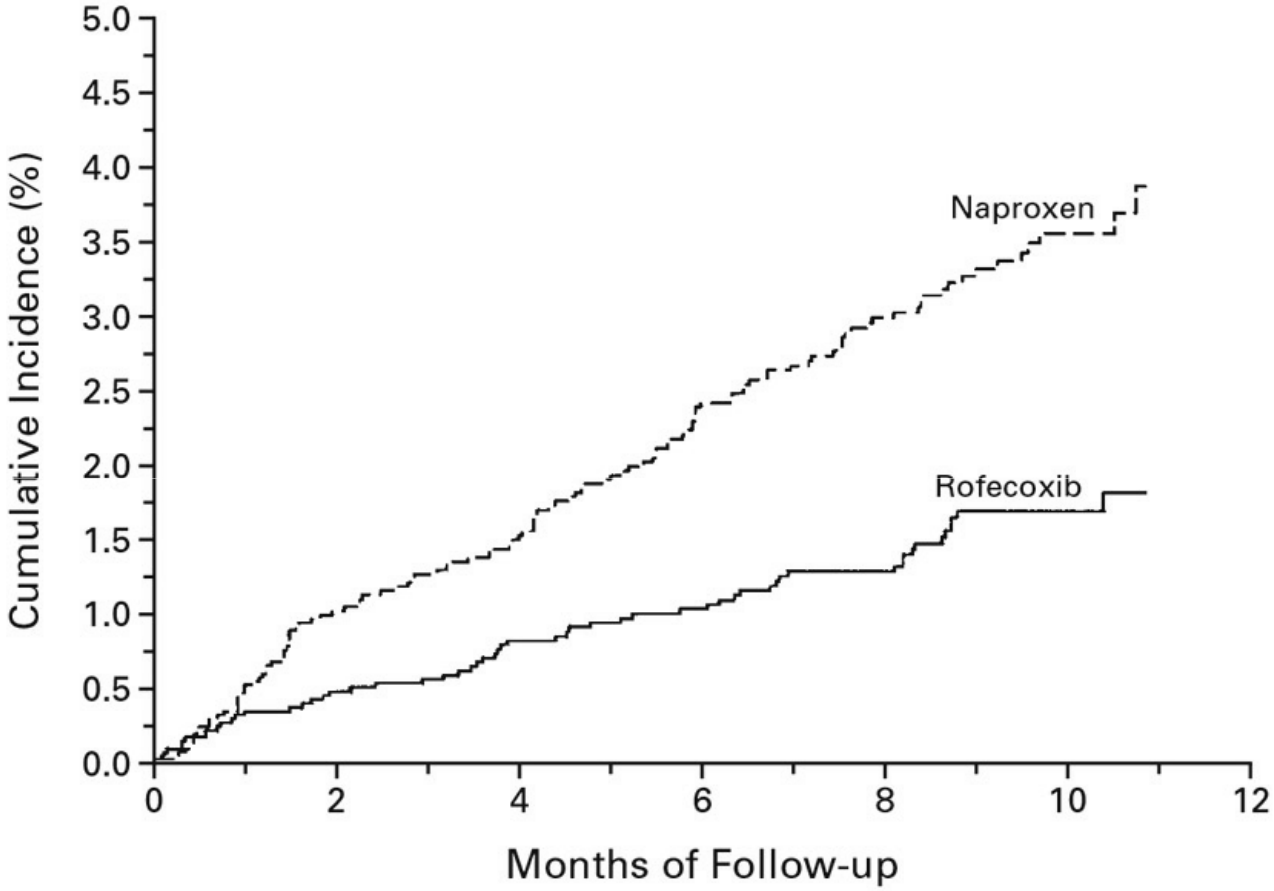
OUT OF 383 CLINICAL TRIALS

64 % COULD DETECT A DIFFERENCE > 50 %

84 % COULD DETECT A DIFFERENCE > 25 %

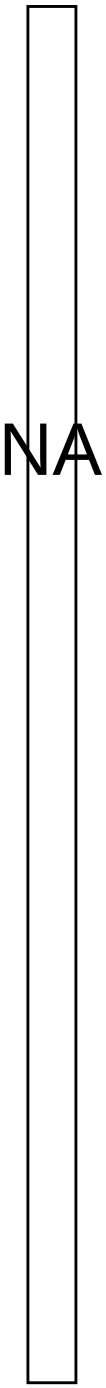
MOHER et al., 1994

Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.



No. at Risk							
Rofecoxib	4047	3641	3402	3180	2806	1073	533
Naproxen	4029	3644	3389	3163	2796	1071	513

Vigor Study Group. N Engl J Med 2000



	CARDIOVASCULAR TOXICITY
DICLOFENAC	1
COXIBs	0.92* (0.81-1.05)

* 26 RCT

Psaty and Weiss, 2007

	CARDIOVASCULAR TOXICITY
NAPROXEN	1
COXIBs	1.57* (1.21-2.03)

* 42 RCT

Psaty and Weiss, 2007

	CARDIOVASCULAR TOXICITY
PLACEBO	1
COXIBs	1.42* (1.13-1.76)

* 121 RCT

THERAPEUTIC STRATEGIES MAY INVOLVE NON-PHARMACOLOGICAL INTERVENTIONS

- PSYCHOTHERAPIES
- EXERCISE
- DIETS

NEED TO ESTABLISH THEIR VALIDITY AS AN ALTERNATIVE OR AN ADDITION TO DRUG TREATMENTS

WHICH PRIORITIES?

Control of trials performed by pharmaceutical industries

Studies that are likely not to be performed by pharmaceutical companies

- Rare diseases and orphan drugs

- Sub populations excluded by clinical trials

- Diseases of developing countries

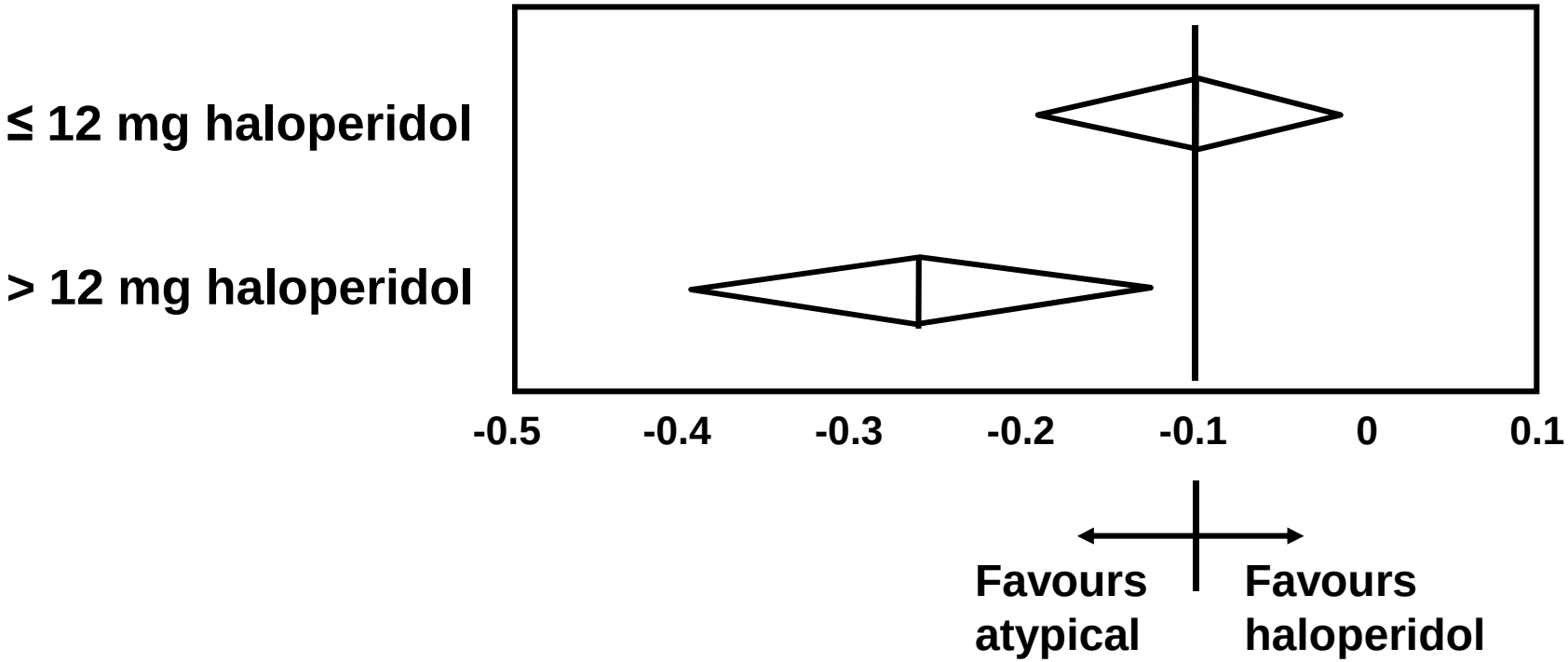
- Studies to decrease the NNT

- Generics

Head to head comparisons

- Single drugs and therapeutic strategies

Active pharmacovigilance



Drop out rates by dose of comparator drug in trials of patients with schizophrenia or related disorders (risk difference and 95 % confidence intervals)

Geddes et al., 2000

PARAMETER	OLANZAPINE vs PERPHENAZINE	
NEUROLOGIC EFFECTS	14%	17%0
WEIGHT GAIN	30%	12%0
BLOOD GLUCOSE (CHANGE)	15 ± 20	5.2 ± 200
GLYCOSYLATED Hb	00.4 ± 0.09	0.1 ± 0.06
CHOLESTEROL (CHANGE)	9.7 ± 2.2	0.5 ± 2.30
TRIGLYCERIDES (CHANGE)	42 ± 8	8 ± 11

CATIE, 2005

Quality, efficacy, safety

Necessary, not always sufficient

PRIORITIES IN LEGISLATION

ADDED VALUE FOR NEW MEDICINES

ONE OF THE 2 PHASE3 RCT BY INDEPENDENT ORGANIZATIONS

FUND TO SUPPORT INDEPENDENT RCT

The fund for independent research at AIFA

(Art. 48, law 326/2003)

Promotion of independent research is among the missions of AIFA

Pharmaceutical companies are obliged to devote 5% of their promotional expenditure to a fund for independent research

The research topics funded by AIFA

Relevance for the NHS

Chronic limitations of private funding:

- rarity of diseases
- patients generally excluded from RCTs
- drugs whose patent is expired

Studies that will likely not to be supported by pharmaceutical companies

The call for proposals

AREA 1

Orphan drugs for rare diseases and drugs for non-responders

AREA 2

Comparison among drugs and therapeutic strategies

AREA 3

Strategies to improve the appropriateness of drug use and pharmacoepidemiology studies

	2006	2007	2008
LETTERS OF INTENT	402	454	360
SELECTED PROJECTS	101	099	-
FUNDED PROJECTS	054	051	-

	N. OF PROJECTS	
	2006	2007
ORPHAN DRUGS	20	24
HEAD TO HEAD COMPARISONS	13	16
OUTCOME AND PHARMACOVIGILANCE	21	11
TOTAL	54	51
SUPPORT M €	35	31

SOME TOPICS AIFA RESEARCH 2007

EVALUATION OF BENEFIT-RISK PROFILE IN THE USE OF DRUGS
IN PREGNANT WOMEN

STUDIES ON BENEFIT-RISK PROFILE OF LONG TERM
USE OF ANTIVIRAL DRUGS

EVALUATION OF PSYCHO DRUGS COMBINED WITH PSYCHOTHERAPIES

SOME TOPICS AIFA RESEARCH 2007

PHARMACOLOGICAL TREATMENTS OF DEPENDENCE INDUCED BY DRUGS OF ABUSE

LONG TERM BENEFIT-RISK OF TREATMENTS FOR HYPOTHYROID PATIENTS

SOME TOPICS AIFA RESEARCH 2007

COMPARISON OF CARDIOVASCULAR, ANTIDIABETIC AND ANTIASMATHIC DRUGS IN CHILDREN

OPTIMIZATION IN THE USE OF ANESTETHICS AND MYORELAXANTS IN SURGERY

STRATEGIES TO REDUCE FRACTURES IN ELDERLY

SOME TOPICS AIFA RESEARCH 2007

EFFICACY OF CARDIOVASCULAR DRUGS
IN THE FEMALE POPULATION

COMPARISON OF DRUGS IN THE TREATMENT
OF AUTOIMMUNE DISEASES

OPTIMIZATION OF PAIN THERAPY IN NEOPLASTIC PATIENTS

SOME TOPICS AIFA RESEARCH 2007

PREVENTION AND TREATMENT OF SEPSIES

COMPARISON OF GASTROPROTECTIVE AGENTS IN ELDERLY

COMPARISON OF THERAPEUTIC STRATEGIES IN PARKINSON