

THE BIAS OF CLINICAL TRIALS THE NEED
OF INDEPENDENT CLINICAL RESEARCH



Krakow 19th November 2007

CLINICAL TRIALS ARE THE CORNERSTONE
OF EVIDENCE BASED MEDICINE

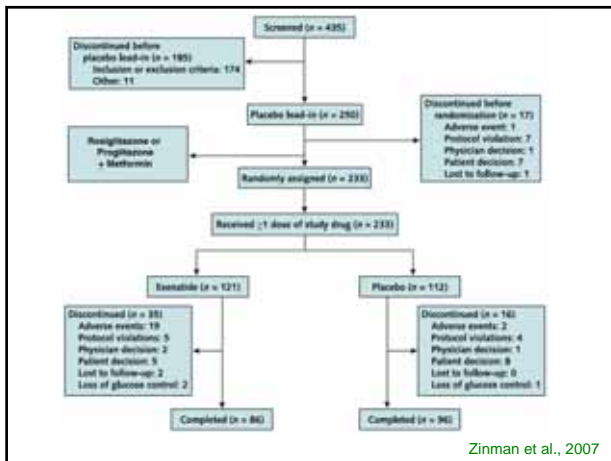
- PHASE 1 TOLERABILITY
- PHASE 2 EFFICACY
- PHASE 3 BENEFIT-RISK

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

HUGE COMMERCIAL INTEREST MAY
MANIPULATE CLINICAL TRIALS INTRODUCING
A BIAS THAT AFFECTS THEIR OUTCOME

- THE EXCESSIVE USE OF PLACEBO

PLACEBO SHOULD BE USED ONLY WHEN
THERE ARE NO EFFECTIVE DRUGS FOR
A GIVEN INDICATION INAPPROPRIATE USE
OF PLACEBO MAY LEAD TO AN OPTIMISTIC
EVALUATION OF A NEW DRUG



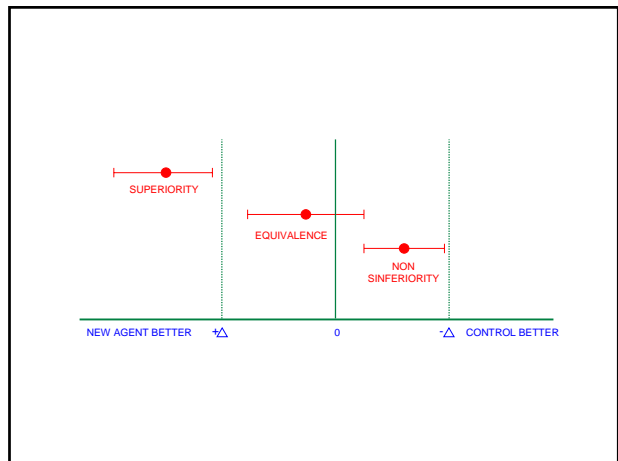
Estimates of Mean Changes in Efficacy Measures from Baseline to Week 16*			
Efficacy Measure	Exenatide Group (n = 121)	Placebo Group (n = 112)	Difference (95% CI)†
Hemoglobin A_{1c} level			
Baseline level, %	7.89	7.91	
Change from baseline to week 16, %	-0.89	0.09	-0.98 (-1.21 to -0.74)
Fasting plasma glucose level			
Baseline level, mmol/L	9.13	8.84	
Change from baseline to week 16, mmol/L	-1.59	0.10	-1.69 (-2.22 to -1.17)
Mean daily self-monitored blood glucose level			
Baseline level, mmol/L	9.46	9.18	
Change from baseline to week 16, mmol/L	-1.85	-0.14	-1.71 (-2.09 to -1.33)
Daily mean postprandial self-monitored blood glucose level			
Baseline level, mmol/L	1.74	1.99	
Change from baseline to week 16, mmol/L	-1.58	-0.31	-1.27 (-1.64 to -0.91)
Body weight			
Baseline, kg	97.53	96.75	
Change from baseline to week 16, kg	-1.75	-0.24	-1.51 (-2.15 to -0.88)

A FAIR COMPARISON WOULD HAVE BEEN TO USE INSTEAD OF PLACEBO ONE OF THE MANY ANTIADIBETIC AGENTS AVAILABLE ON THE MARKET

• DESIGN OF CLINICAL TRIALS

CLINICAL TRIALS MAY BE DESIGNED TO DEMONSTRATE

- SUPERIORITY
- EQUIVALENCE
- NON INFERIORITY



Setting δ , the maximum difference between two antidepressant drugs accepted as a demonstration of equivalence in published trials comparing SSRI, TCA and placebo

Reference	Antidepressant drug	Sample Size	δ
Feighner et al., 1989a	Fluvoxamine, imipramine, PLO	86	40%
Feighner et al., 1989b	Fluoxetine, imipramine, PLO	178	30%
March et al., 1990	Fluvoxamine, imipramine, PLO	54	63%
Dunbar et al., 1991	Paroxetine, imipramine, PLO	717	16%
Shrivastave et al., 1992	Paroxetine, imipramine, PLO	120	39%
Doogan & Langdon, 1994	Sertraline, dothiepine, PLO	308	23%

PLO = Placebo

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

• INCLUSIONS AND EXCLUSION OF PATIENTS

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

A Systematic Sampling Review

Harriette C. 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 %)

14 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

- INADEQUATE COMPARATOR

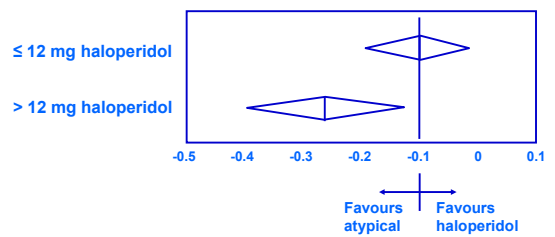
TACROLIMUS VS CYCLOSPORINE

32.5 % 51.3 %

ACUTE REJECTIONS

ACUTE RENAL REJECTIONS ARE MINIMIZED
 WHEN TROUGH LEVELS ARE KEPT BETWEEN
 330 - 430 ng/ml

MARGREITER et al., 2002 TRIAL
 CYCLOSPORINE < 300 ng/ml



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

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

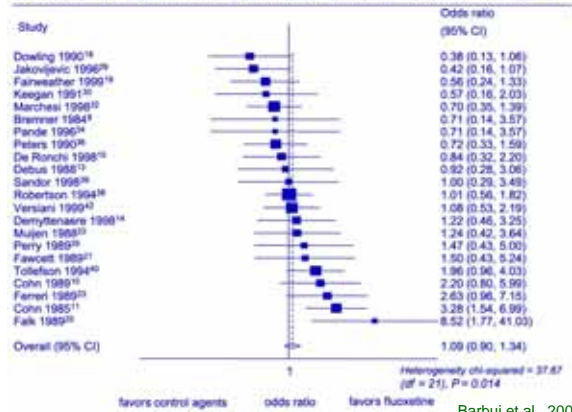
CARDIOVASCULAR TOXICITY

PLACEBO 1

COXIBs 1.42*
(1.13-1.76)

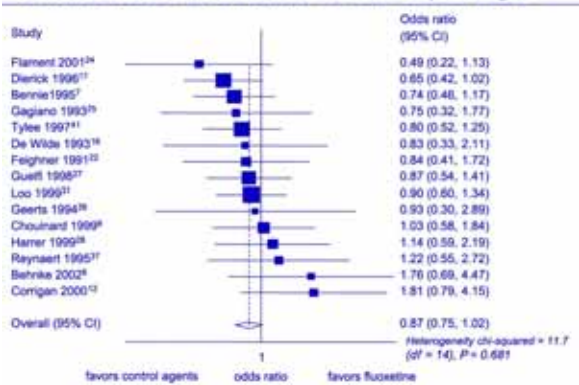
* 121 RCT

Outcome of RCTs where fluoxetine was the experimental agent.



Barbui et al., 2004

Outcome of RCTs where fluoxetine was the comparator agent.



Barbui et al., 2004

• SURROGATE END POINTS

QUALITY OF LIFE, MORBILITY, MORTALITY SHOULD BE THE FINAL OBJECTIVES OF CLINICAL TRIALS

- ENCAINIDE AND FLECAINIDE DECREASE ARRHYTHMIAS BUT INCREASE MORTALITY
- OESTROGENS INCREASE HDL-CHOLESTEROL BUT DO NOT PREVENT CARDIOVASCULAR EVENTS
- TORCETRAPIB INCREASES HDL-CHOLESTEROL BUT INCREASES MORTALITY

**HbA_{1c} IS NOT A SURROGATE END-POINT FOR
CARDIOVASCULAR DISEASES IN TYPE 2 DIABETES**

SULFONYLUREAS	HbA _{1c} ↓	MYOCARDIAL INFARCTION ↑
ROSIGLITAZONE	HbA _{1c} ↓	HEART FAILURE ↑

NEED TO EVALUATE PARAMETERS IMPORTANT FOR PATIENTS

Primary efficacy end points of the main studies
supporting 27 indications

	No.	%
Overall survival	2	7
TTP/PFS	11	41
Response rate	13	48
Other ^a	1	4

TTP = time to progression; PFS = progression-free survival.

^aApproval without empirical data, supported by bibliographic review of nonclinical and clinical data.

APOLONE et al., 2005

Evaluation of anticancer drugs by EMEA from 1995 to 2004:
summary of the 48 studies used as basis for approval

Clinical trial design (48 trials)	Type of end point (primary) (48 trials)	Difference in survival, when available (13 trials)
RCT 25	Survival 4	Range 0–3.7 months
SAT 19	Resp. rate 30	Mean 1.5 (months)
NC-RCT 4	TTP/PFS 14	Median 1.2 (months)

RCT = randomised clinical trial; SAT = single-arm trial; NC-RCT = noncomparative RCT; TTP = time to progression; PFS = progression-free survival.

APOLONE et al., 2005

USE OF SURROGATE END-POINT FOR DRUG APPROVAL
IS UNETHICAL WHEN THERE ARE ALREADY PRODUCTS
SUBMITTED TO TRIALS WITH HARD END-POINTS
EXAMPLES: STATINS, ANTIDIABETICS, ANTIHYPERTENSIVES

- UTILIZATION OF COMPOSITE END-POINTS

BMJ Composite and surrogate outcomes in
randomised controlled trials

Nick Freemantle and Mel Calvert

BMJ 2007;334:756-757
doi:10.1136/bmj.39176.461227.80

For example, a statement that an intervention reduces a composite end point of cardiovascular mortality, myocardial infarction, and revascularisation procedures is misleading if revascularisation procedures were more common outcomes than death or infarction, or if the intervention had a large apparent treatment effect on revascularisation but not on death or infarction.

Breakdown of how individual components contribute to the composite primary endpoint of death, recurrent ischaemia, or coronary-artery occlusion

	Clopidogrel (n=1752)	Placebo (n=1739)	p
Death	45 (2.6%)	38 (2.2%)	0.49
Recurrent ischaemia	44 (2.5%)	63 (3.8%)	0.08
Coronary-artery occlusion*	192 (11.7%)	301 (18.4%)	<0.001
Composite primary endpoint	262 (15.0%)	377 (21.7%)	<0.001

*TIMI grade 0 or 1 on angiography.

Lapostolle et al., 2007

The DREAM trial, of rosiglitazone in the prevention of diabetes in patients with impaired fasting glucose or glucose tolerance (or both), had the composite primary outcome measure of diabetes or death. The primary outcome was highly statistically significant, although there was no difference in the rate of death between the groups (30/2635 (1.1%) in the rosiglitazone group and 33/2634 (1.3%) in the placebo group). If the FDA followed standard practice, it would react to an application for extension of the marketing authorisation by granting authorisation for the composite outcome. To do so would wrongly endorse the idea that mortality was reduced.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trialists use composite end points, outcomes that capture the number of patients who have one or more of several events, to increase event rates and statistical power. When the gradient of importance to patients is large, and the more important events are uncommon and show negligible treatment effects, use of composite end points can be misleading.

WHAT THIS STUDY ADDS

Almost half of a sample of recent prominently published cardiovascular trials used composite end points, which were often inadequately reported and showed large gradients in importance to patients.

End points of least importance to patients typically contributed most events.

Composite end points, as currently used in cardiovascular trials, may often be misleading.

Ferreira-González et al., 2007

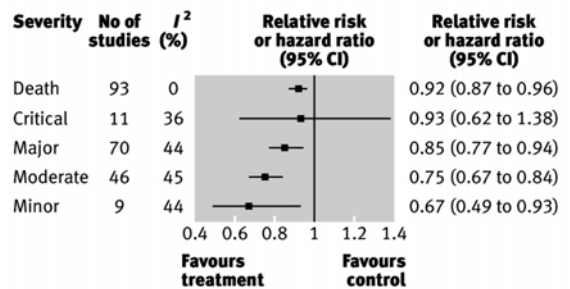
Primary and Secondary Outcomes

End Point	No. (%) of Patients With an Event		Hazard Ratio (95% CI) ^a	P Value ^b
	Warfarin Group ^c (n = 1022)	Placebo Group ^c (n = 1028)		
Primary outcome				
All-cause mortality	448 (43)	430 (42)	1.04 (0.91-1.18)	.61
Secondary outcomes				
MI (fatal and nonfatal)	128 (12)	130 (13)	0.88 (0.67-1.16)	.38
Stroke (fatal and nonfatal)	37 (3)	41 (4)	0.90 (0.58-1.43)	.64
Angioplasty	60 (6)	53 (5)	1.14 (0.79-1.65)	.50
Composite of all-cause mortality, MI, stroke, or angioplasty	623 (61)	620 (61)	1.03 (0.89-1.17)	.70
Deaths in advanced chronic kidney disease patients only (n = 170)	368 (65)	340 (63)	1.07 (0.62-1.74)	.80
Revascularisation in percutaneous coronary intervention patients (n = 1267)	146 (12)	162 (13)	1.01 (0.61-1.70)	.97

^a folic acid + B6 + B12

Variability in magnitude of the effect of intervention across categories of importance to patients

COMPOSITE END-POINTS



Ferreira-González et al., 2007

- FOCUS ON SELECTIVE ADVERSE REACTIONS

ATYPICAL ANTIPSYCHOTICS

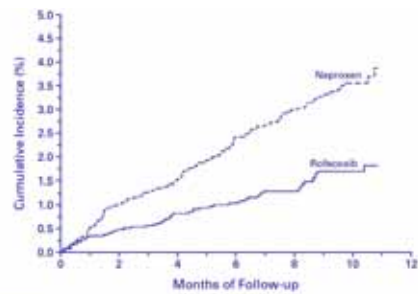
THE REDUCED EFFECT ON EPS IS THE
FOCUS OF ADVERTISEMENT
WEIGHT GAIN AND PROPENSITY TO DIABETES ?

PARAMETER OLANZAPINE vs PERPHENAZINE

NEUROLOGIC EFFECTS	14%	17%
WEIGHT GAIN	30%	12%
BLOOD GLUCOSE (CHANGE)	15 ± 2	5.2 ± 2
GLYCOSYLATED Hb	0.4 ± 0.09	0.1 ± 0.06
CHOLESTEROL (CHANGE)	9.7 ± 2.2	0.5 ± 2.3
TRIGLYCERIDES (CHANGE)	42 ± 8	8 ± 11

CATIE, 2005

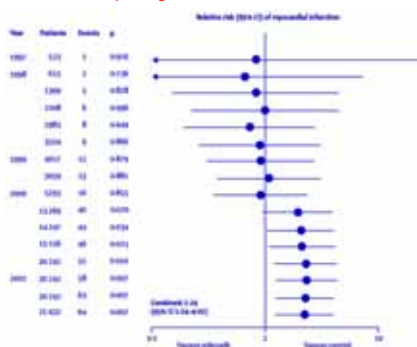
Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Event among All Randomized Patients.



No. at Risk						
Rofecoxib	4047	3641	3422	3180	2806	1073
Naproxen	4029	3648	3388	3183	2795	1073

Vigor Study Group, N Engl J Med 2000

Cumulative meta-analysis of randomised trials comparing rofecoxib with control



Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Peter Juni et al, Lancet 2004

For newly licensed drugs,
confidence about safety can only be provisional

Rofecoxib

- at the time of marketing approval (1999):
safety data based on 5,000 patients
- at the time of withdrawal (2004):
given daily to 2,000,000 patients
(sales in 2003 US \$ 2.5 billion)

- SELECTIVE PUBLICATIONS

SELECTIVE PUBLICATIONS OF 5 SSRI

EVIDENCE B(I)ASED MEDICINE

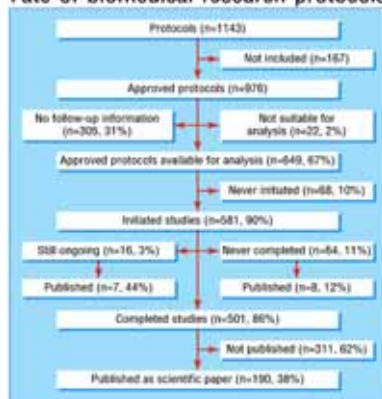
IN TOTAL 42 STUDIES

- 21 STUDIES SHOW DRUG BETTER THAN PLACEBO
 - 19 PRIMARY PUBLICATIONS
- 21 STUDIES SHOW NEGATIVE RESULTS
 - 6 PRIMARY PUBLICATIONS

Swedish Drug Regulatory Authority

Melander et al., BMJ 2003

Fate of biomedical research protocols



Decullier et al., 2005

SELECTIVE REPORTING OF CLINICAL TRIALS MAY BIAS META-ANALYSES AND MISDIRECT GUIDE-LINE. IN A RETROSPECTIVE REVIEW OF 130 TRIALS, THOSE WITH POSITIVE RESULTS WERE THREE TIMES MORE LIKELY TO BE PUBLISHED WITH A SIGNIFICANT SHORTER TIME TO PUBLICATION THAN THOSE WITH NEGATIVE RESULTS.

STERN, SIMES, 1997

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil
 Asbjørn Hróbjartsson, MD, PhD
 Mette T. Haahr, BSc
 Peter C. Gøtzsche, MD, DrMedSci
 Douglas G. Altman, DSc

JAMA, May 26, 2004—Vol 291, No. 20 2457

Results

One hundred two trials with 122 published journal articles and 3736 outcomes were identified.

Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported.

An Wen Chan et al., 2004

**BIAS IN CLINICAL TRIALS
MAY BE DETERMINED BY:**

- CONFLICT OF INTEREST

Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the *BMJ*

Lise L. Kjaergard, Bodil Als-Nielsen

Conclusions Authors' conclusions in randomised clinical trials significantly favoured experimental interventions if financial competing interests were declared. Other competing interests were not significantly associated with authors' conclusions.

Outcome of Studies by Support of Research

Outcome of Study	Studies Supported by a Drug Company (n = 40)	Studies Not Supported by a Drug Company (n = 112)
	n(%)	
Favorable	39 (98)	89 (79)
Not favorable	1 (2)	23 (21)

Cho and Bero, 1996

	Outcome		
	Favourable	Neutral	Unfavourable
Sponsorship v. outcome favouring SSRIs over TCAs: industry v. non-industry studies			
Industry sponsor	13	4	0
Non-industry sponsor	1	2	3
Sponsorship v. outcome favouring newest antidepressant: industry v. non-industry studies			
Industry sponsor	25	7	1
Non-industry sponsor	1	2	4
Sponsorship v. outcome favouring newest antidepressant: industry v. non-industry modelling studies			
Industry sponsor	18	0	1
Non-industry sponsor	1	1	3

Baker et al., 2003

- THE EUROPEAN LEGISLATION

Institutional location

Industry, consumers or public health?

Quality, efficacy, safety

Necessary, not always sufficient

CONFIDENTIALITY

- IS JUSTIFIED?
- MINORITY POSITION
- REASONS FOR WITHDRAWAL
- RESULTS OF COMMITMENTS

COMMITMENTS GIVEN BY COMPANIES AT THE TIME OF APPROVAL OF A DRUG TO CONDUCT FURTHER EFFICACY OR SAFETY STUDIES ONCE THE DRUG IS ON THE MARKET ARE RARELY ENFORCED.
OUT OF 2701 POST-MARKETING COMMITMENTS ONLY 926 (34.3%) WERE HONOURED ACCORDING TO FDA.
WHAT ABOUT EMEA?

LACK OF REQUIREMENTS FOR ADDED VALUE DOES NOT ALLOW COMPARATIVE EVALUATION IN ORDER TO PLACE NEW DRUGS IN THE CONTEXT OF CURRENT

AS A CONSEQUENCE OF THE IMPORTANT BIAS IN RCT THE BENEFIT/RISK RATIO OF NEW DRUGS IS CONSIDERABLY OVERESTIMATED

CONCLUSIONS

- INTRODUCE THE NEED TO DEMONSTRATE AN ADDED VALUE FOR NEW MEDICINAL PRODUCTS
- ALL NEW DRUGS SHOULD HAVE AT LEAST 2 PHASE 3 TRIALS
- ONE OF THE PHASE 3 TRIALS SHOULD BE CARRIED OUT BY AN INDEPENDENT ORGANIZATION
- ABOLISH CONFIDENTIALITY OF PHARMACOLOGICAL AND CLINICAL DATA UTILIZED FOR DRUG APPROVAL
- A FUND TO SUPPORT INDEPENDENT CLINICAL TRIALS SHOULD BE ESTABLISHED
- FOR VERY EXPENSIVE DRUGS REIMBURSEMENT SHOULD BE MADE ONLY ON THE BASIS OF EFFICACY IN SINGLE PATIENTS

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

Peer review process

Each study protocol is evaluated by :

- 2 independent members who wrote a comment
- 1 discussant
- Through a process of consensus seeking, the committee arrives at a numeric rating for each proposal

The scoring system

- Final score: 1.0-5.0
 - 1.0-2.9: insufficient
 - 3.0-3.9: sufficient / low priority
 - 4.0-5.0: excellent / high priority
- Final ranking by topic and area

	2006	2007	2008
LETTERS OF INTENT	402	454	360
SELECTED PROJECTS	101	99	-
FUNDED PROJECTS	54	51	-

	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

EXAMPLES OF APPROVED PROJECTS

A prospective study on long-term outcome and potential usefulness of an intervention aimed at reducing adverse effects in patients with refractory epilepsy.

Evaluation of prescribing pattern and safety profile of antidepressant and antipsychotic medications in Italian general practice.

Pharmacist's outreach visits and new information formats: cluster and single-doctor randomised controlled trials for evaluating their feasibility and impact on knowledge, attitudes and prescribing practices of general practitioners in three Italian regions.

EXAMPLES OF APPROVED PROJECTS

A randomized, placebo-controlled study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins.

A randomized prospective, multicenter trial to compare the effect on chronic allograft nephropathy of mycophenolate mofetil versus azathioprine as the sole immunosuppressive therapy for kidney transplant recipients.

A randomized, controlled trial to evaluate the efficacy of low-molecular-weight heparin on pregnancy outcome of women with previous pregnancy complications.

EXAMPLES OF APPROVED PROJECTS

First adjuvant trial on all aromatase inhibitors in early breast cancer.
A phase 3 study comparing anastrozole, letrozole and exemestane, upfront or sequentially.

A randomized clinical trial of trastuzumab optimization in patients with locally advanced and/or metastatic breast cancer overexpressing HER2 after a first-line chemotherapy plus trastuzumab.

Multicenter randomized controlled study of azathioprine versus interferon beta in relapsing-remitting multiple sclerosis.

TO ESTABLISH THE TOPICS OF THE YEARLY CALL HEARINGS OF SCIENTIFIC SOCIETIES AND STOCKHOLDERS ARE MADE.
A WEBB SITE IS AVAILABLE TO COLLECT SUGGESTIONS

- 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 ANTIASMATIC DRUGS IN CHILDREN
- OPTIMIZATION IN THE USE OF ANESTHETICS 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 SEPSIS
- COMPARISON OF GASTROPROTECTIVE AGENTS IN ELDERLY
- COMPARISON OF THERAPEUTIC STRATEGIES IN PARKINSON