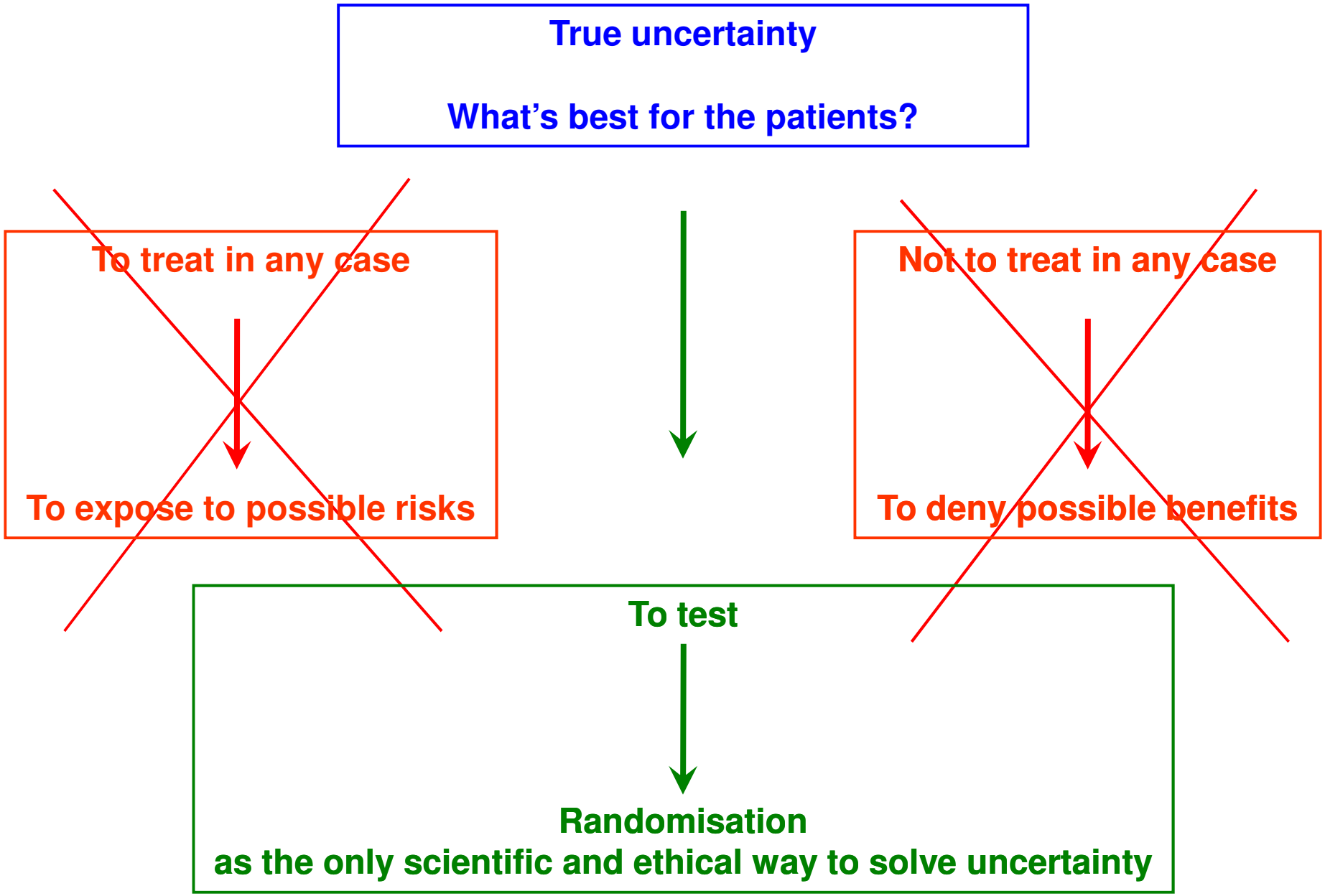
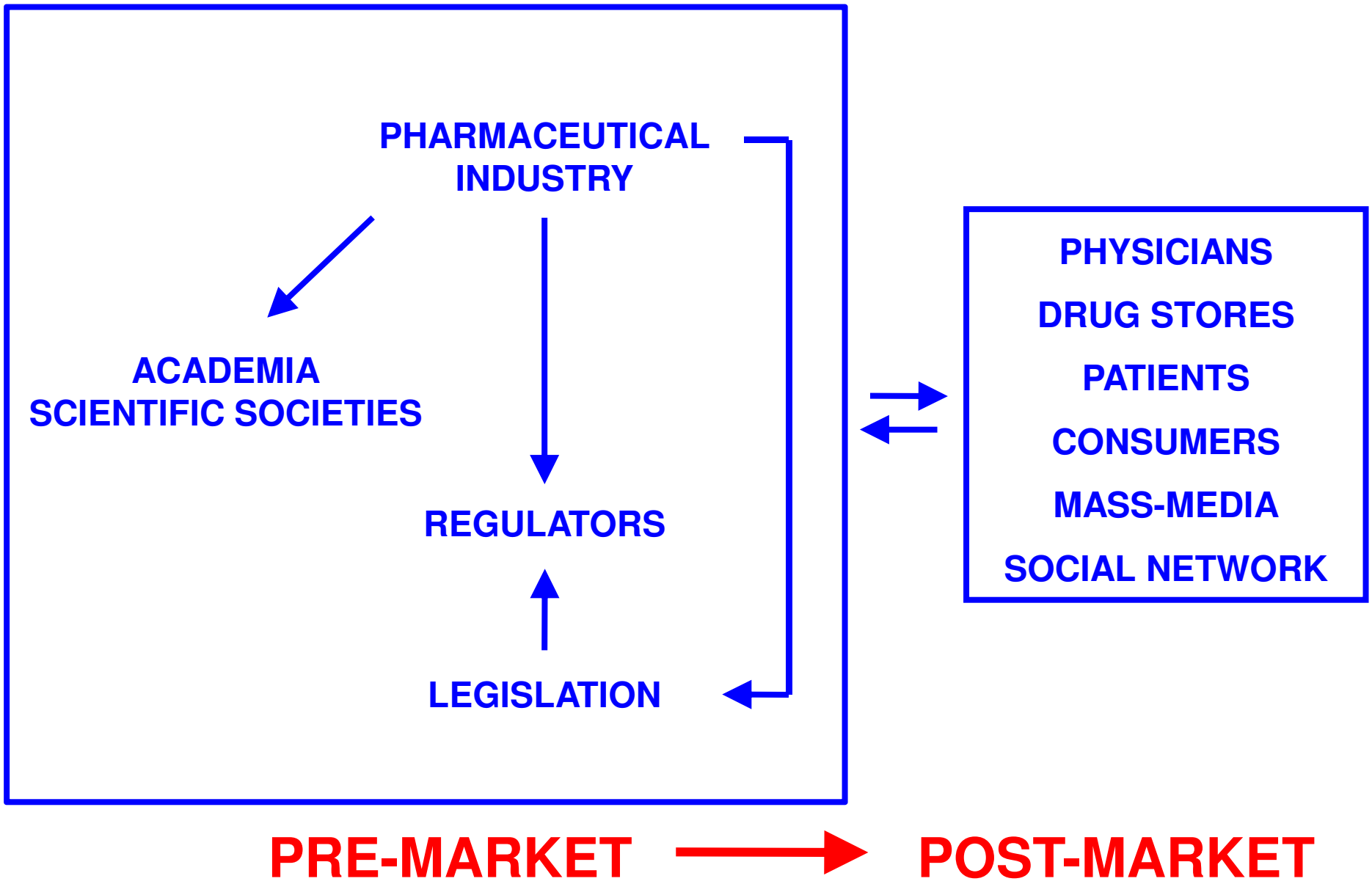
BIAS NEGLI STUDI CLINICI CONTROLLATI

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI IRCCS

SILVIO GARATTINI

Roma, 17 Novembre 2015


True uncertainty
What's best for the patients?
To treat in any case
To expose to possible risks
Not to treat in any case
To deny possible benefits
To test
Randomisation
as the only scientific and ethical way to solve uncertainty


PHARMACEUTICAL INDUSTRY
ACADEMIA SCIENTIFIC SOCIETIES
REGULATORS
LEGISLATION
PHYSICIANS
DRUG STORES
PATIENTS
CONSUMERS
MASS-MEDIA
SOCIAL NETWORK
PRE-MARKET
POST-MARKET

IMPROVEMENT INDUCED BY 281 NEW MEDICINAL PRODUCTS

MEDIAN	**0,097 QALY**
51%	**≤ 0,1 QALY**
12%	**≥ 1,0 QALY**

Basic Clin Pharmacol
2009, 105, Suppl. 1, 032

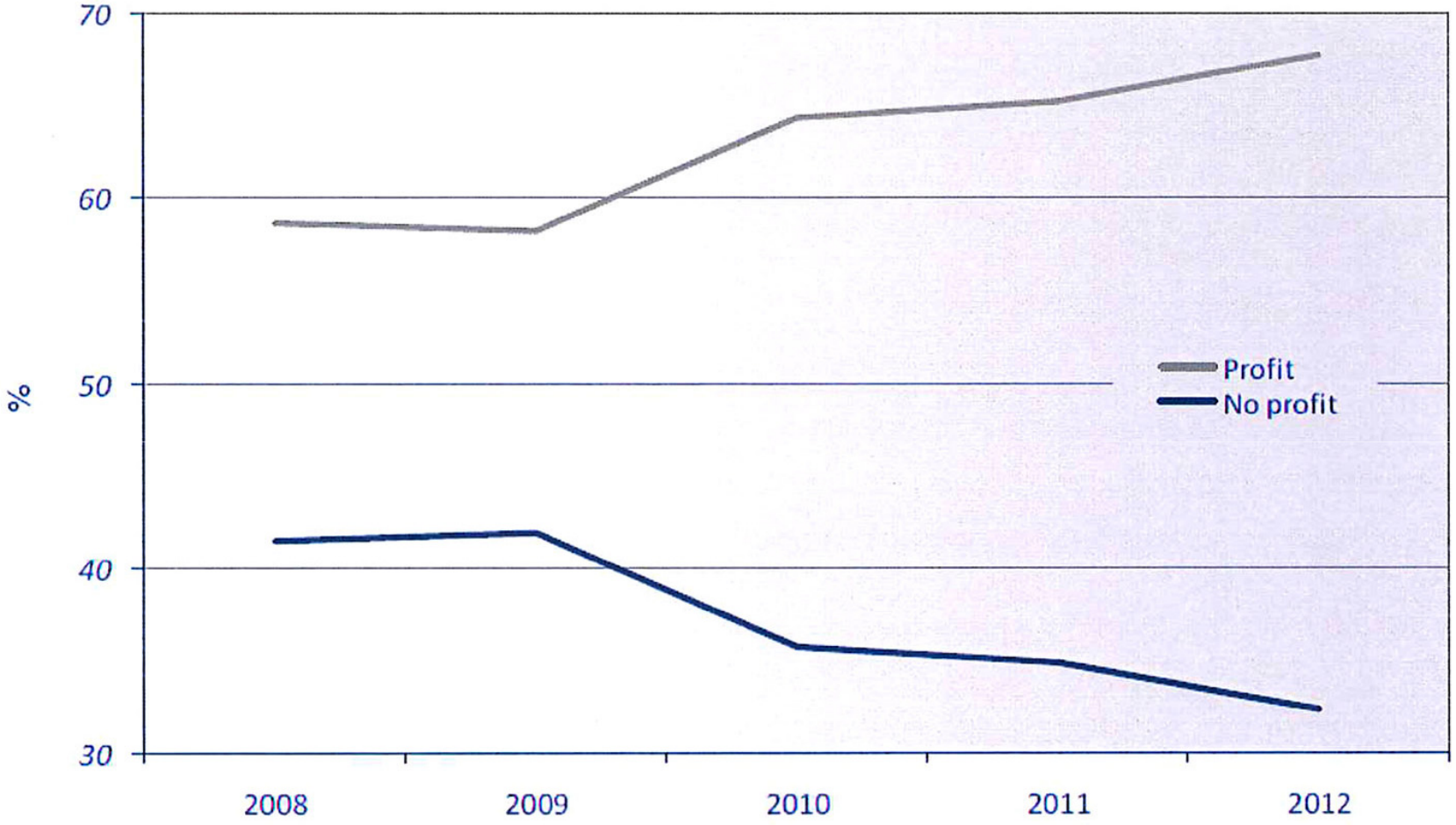
Walker et al., 2009

EMA Conditional Approvals (2006-2014) and their Prescrire ratings (per indication)

Prescrire Rating	Number of drugs	Percentage
Bravo	0	0
A real advance	0	0
Offers an advantage	4	19
Possibly helpful	4	19
Nothing new	2	10
Judgment reserved	6	29
Not acceptable	5	24

Clinical trials per year and profit / no profit Sponsors

Total CT: 3,684



Source: 12° National Report on Clinical Trial in Italy- 2013

ITALY

N. of studies non-profit 2008 - 2012

- 38 %

Position of Italy n. of recluted patients

23 rd

Clinical Trial Attractiveness Index

> 30 th

3 KEYWORDS

- EVIDENCE

EVIDENCE

- INAPPROPRIATE USE OF PLACEBO

Characteristics of efficacy evidence supporting approval of supplemental indications for prescription drugs in United States, 2005-14: systematic review

Bo Wang, Aaron S Kesselheim

BMJ 2015;351:h4679

Characteristic	Trial comparators in efficacy studies supporting approval of new drug indications		
	Active comparator	Placebo comparator	No comparator
	Supplemental indications	Supplemental indications	Supplemental indications
Supplement category:			
New indication	41/136 (30)	77/136 (57)	18/136 (13)
Modified indication	47/93 (51)	39/93 (42)	5/93 (5)
Expanded population	7/65 (11)	26/65 (40)	22/65 (34)

Characteristic	Trial comparators in efficacy studies supporting approval of new drug indications		
	Active comparator	Placebo comparator	No comparator
	Supplemental indications	Supplemental indications	Supplemental indications
Chemical type:			
Small molecule	68/209 (33)	98/209 (47)	36/209 (17)
Biologic	27/85 (32)	44/85 (52)	9/85 (11)

RELATIVE RISK REDUCTION OF RELAPSES IN RESPECT TO PLACEBO

IFNβ-1a	32 %	(1996)
IFNβ-1b	28 %	(1995)
GLATIRAMER	29 %	(1995)

RCT CARRIED OUT AGAINST PLACEBO

CLADRIBINE (2010)

NATALIZUMAB (2006)

FINGOLIMOD (2010)

DIRUCOTIDE (2011)

TERIFLUNOMIDE (2011)

LAQUINIMOD (2012)

EXCESS OF RELAPSES THAT COULD BE AVOIDED IF A COMPARATOR WOULD HAVE BEEN USED INSTEAD OF PLACEBO

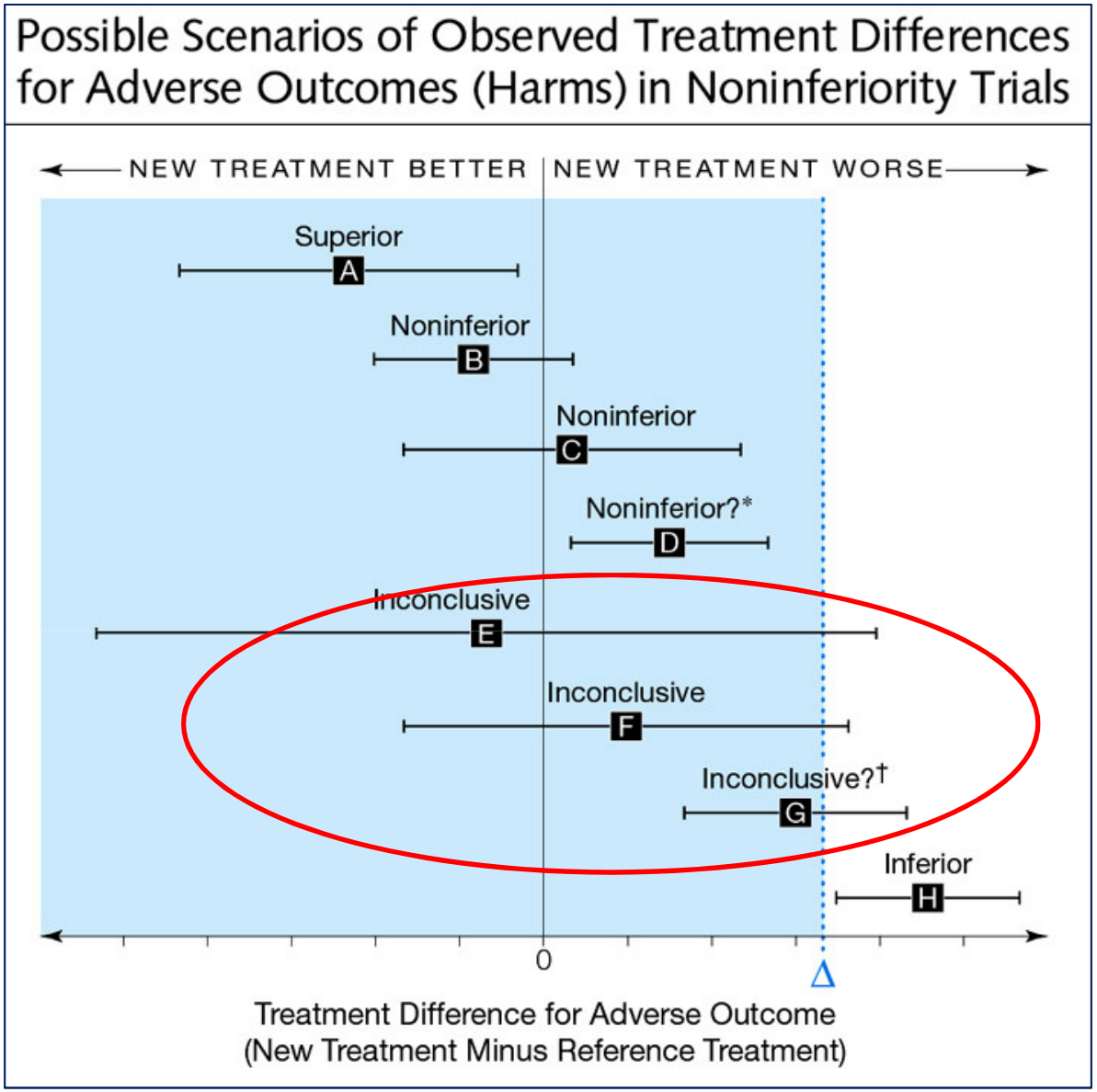
CLADRIBINE	79	DIRUCOTIDE	21
NATALIZUMAB	138	TERIFLUNOMIDE	123
FINGOLIMOD	100	LAQUIMOD	130

TOTAL RELAPSES 591

Garattini et al., 2012

EVIDENCE

- INAPPROPRIATE USE OF PLACEBO
- DESIGN OF NON INFERIORITY



Piaggio et al., 2006

IN THE NON-INFERIOR TYPE OF TRIAL WITH AN ACTIVE CONTROL, INVESTIGATORS ARE TESTING THE NULL HYPOTHESIS THAT A NEW DRUG IS WORSE THAN THE ACTIVE CONTROL (STANDARD) AND WHEN THEY CAN REJECT THE NULL HYPOTHESIS THEY ACCEPT THE ALTERNATIVE, THAT THE NEW DRUG IS NOT WORSE THAN THE ACTIVE CONTROL.

ARAS, 2001
DRUG INFORMATION J.35,1157

CICLESONIDE

POTENZIALI VANTAGGI:

- METABOLITA ATTIVO NEL POLMONE (des-ciclesonide)
- MAGGIORE AFFINITÀ PER IL RECETTORE
- PICCOLE PARTICELLE (1,9 µm)
- UNA SOLA DOSE AL GIORNO

Two studies were described as randomised double-blind parallel group designs (Hiremath 2006; Paunovic 2010) and four studies as randomised double-blind double-dummy parallel group designs (Pedersen 2006; Pedersen 2009; Vermeulen 2007; von Berg 2007). All were designed as non-inferiority studies on lung function.The six studies randomised 3256 children with asthma and included children between the age of 4 and 17 years.

Kramer et al., 2013

New medications should either be more effective, safer or cheaper before they can be recommended for clinical practice. Because older medications have been used for longer periods of time, more knowledge is available on their long-term safety and they are usually cheaper than new drugs (resource use). As far as we are aware there were few data available for the cost-effectiveness of ciclesonide compared to other ICS.

Kramer et al., 2013

Fluticasone/Formoterol Combination Therapy versus Budesonide/Formoterol for the Treatment of Asthma: A Randomized, Controlled, Non-Inferiority Trial of Efficacy and Safety

Anna Bodzenta-Lukaszyk M.D., Roland Buhl M.D., Beatrix Balint M.D., Mark Lomaxd, Kay Spoonerd & Sanjeeva Dissanayake M.D.

Journal of Asthma, 2012, 49:10, 1060-1070

338 NON-INFERIORITY TRIALS
(JANUARY 2012 – JUNE 2014)

98.8 % PROVIDED N.I. MARGINS

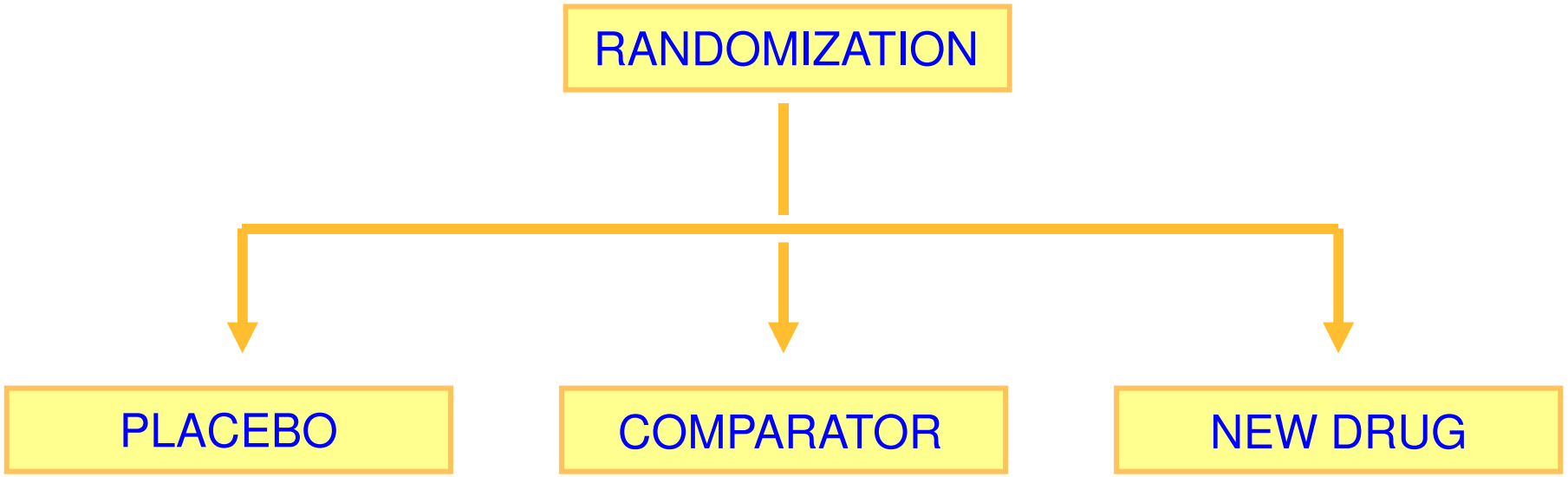
BUT ONLY 27.6 % PROVIDED A JUSTIFICATION FOR THE SELECTED MARGIN

Gopal et al., 2015

Are there specific reasons for allowing a non-inferiority approach?

- There may be non-responders to current treatments and products with comparable activity may offer a useful alternative.
  If the target is non-responders to current treatments, why not test their superiority over drugs with little effect in this subset of patients?

THREE ARM TRIAL



PLACEBO IS NOT NECESSARY IN THE DESIGN OF SUPERIORITY

EVIDENCE

- INAPPROPRIATE USE OF PLACEBO
- DESIGN OF NON INFERIORITY
- SURROGATE END-POINTS

Surrogate Endpoints vs. Clinical Endpoints

Surrogate endpoints used in drug therapy

Therapeutic Class	Surrogates/ Biomarkers	Clinical Endpoint
Antihypertensive	↓ blood pressure	↓ stroke
Glaucoma Rx	↓ intraocular pressure	↓ loss of vision
Osteoporosis Rx	↑ bone density	↓ fracture rate
Antiarrythmia Rx	↓ arrythmias	↑ survival
HIV Rx	↑ CD4 ↓ viral RNA	↓ AIDS progression
Hyperlipidemia Rx	↓ cholesterol	↓ coronary artery dis.
Antidiabetic Rx	↓ HbA1c	↓ morbidity
Antibiotics	negative culture	clinical cure
Prostate cancer Rx	↓ PSA	tumor response

Adapted from: Woodcock J. Biomarkers: Physiological & Laboratory Markers of Drug Effect. Food and Drug Administration, February 1, 2007.

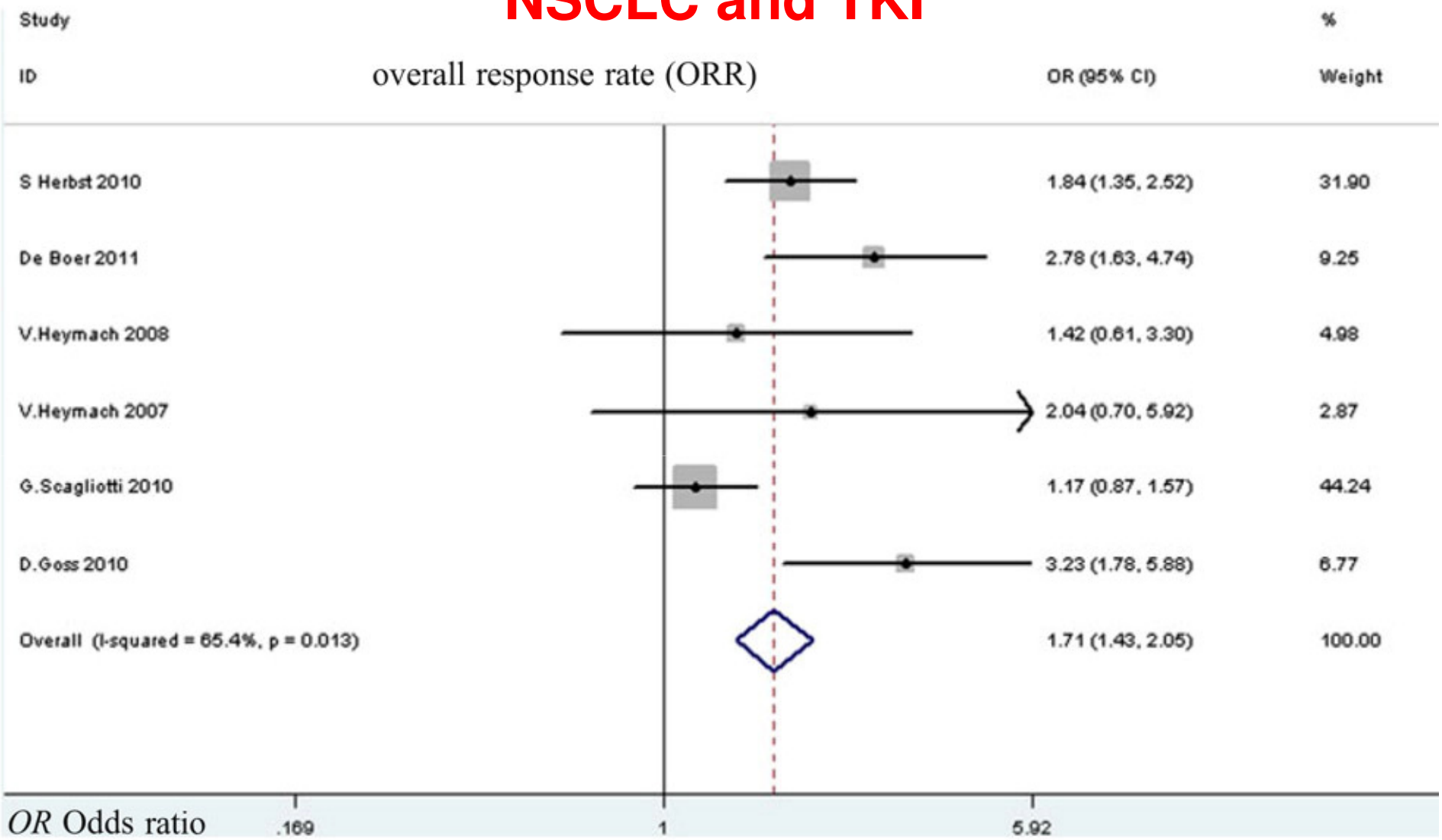
Characteristic	Trial endpoints in efficacy studies supporting approval of new drug indications		
	Clinical outcome	Clinical scale	Surrogate outcome
	Supplemental indications	Supplemental indications	Supplemental indications
Supplement category:			
New indication	44/137 (32)	43/137 (31)	50/137 (36)
Modified indication	28/93 (30)	23/93 (25)	41/93 (44)
Expanded population	14/65 (22)	17/65 (26)	25/65 (38)

Comparison of treatment effects of trials using surrogate outcomes with trials using final patient relevant outcomes: primary and sensitivity analyses

Method of analysis	Risk ratio* (95% CI)	
	Surrogate outcomes	Patient relevant outcomes
Primary analysis:		
Binary outcomes (51 surrogate *v* 83 patient relevant)	0.51 (0.42 to 0.60)	0.76 (0.70 to 0.82)
Sensitivity analyses:		
Inclusion of risk ratios as reported by authors (57 *v* 86)	0.56 (0.48 to 0.65)	0.80 (0.75 to 0.86)
Inclusion of continuous outcomes (84 *v* 101)	0.46 (0.39 to 0.54)	0.68 (0.62 to 0.74)
Binary outcomes, matched pairs (43 *v* 43)	0.48 (0.39 to 0.59)	0.68 (0.61 to 0.77)

Ciani et al., 2013

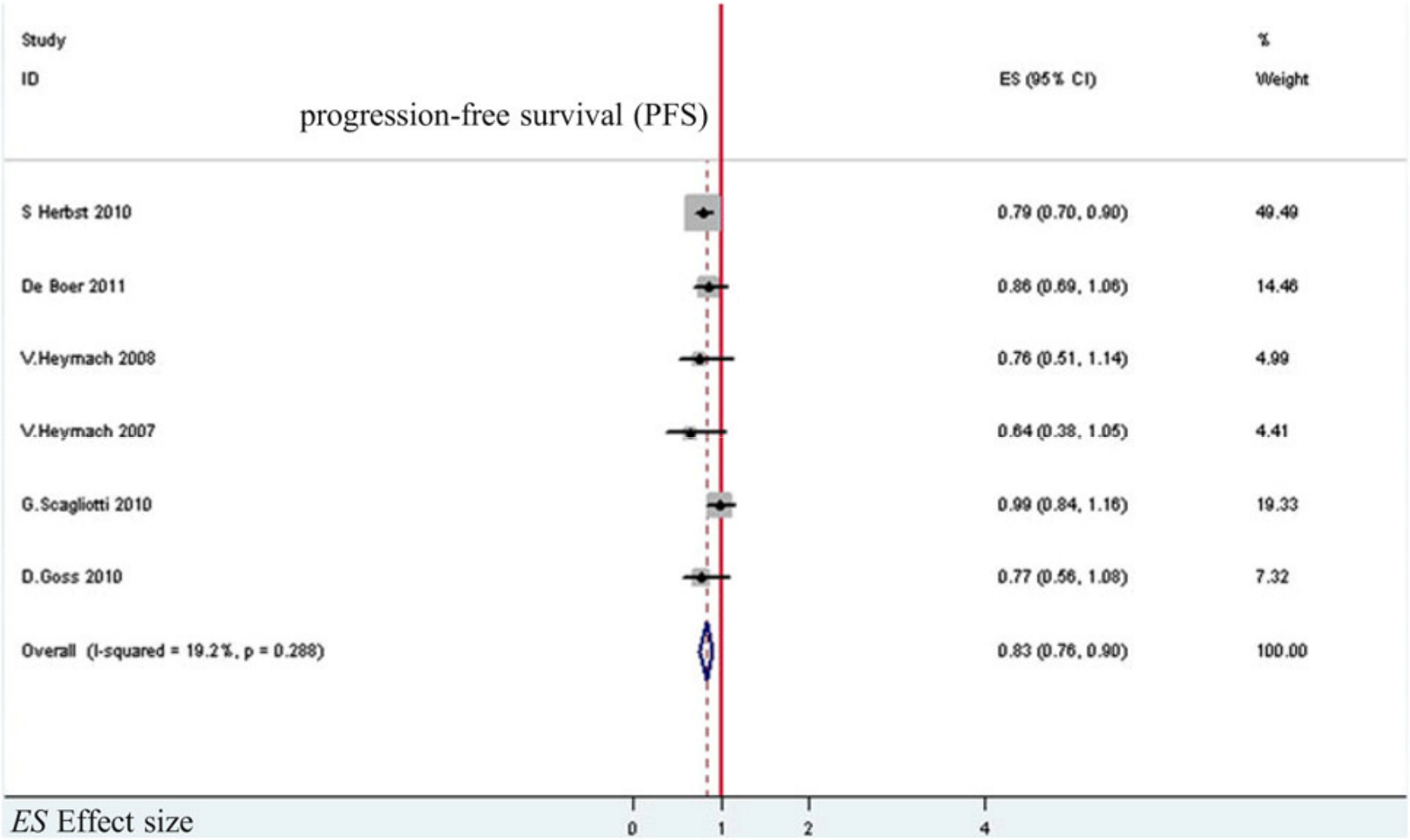
NSCLC and TKI



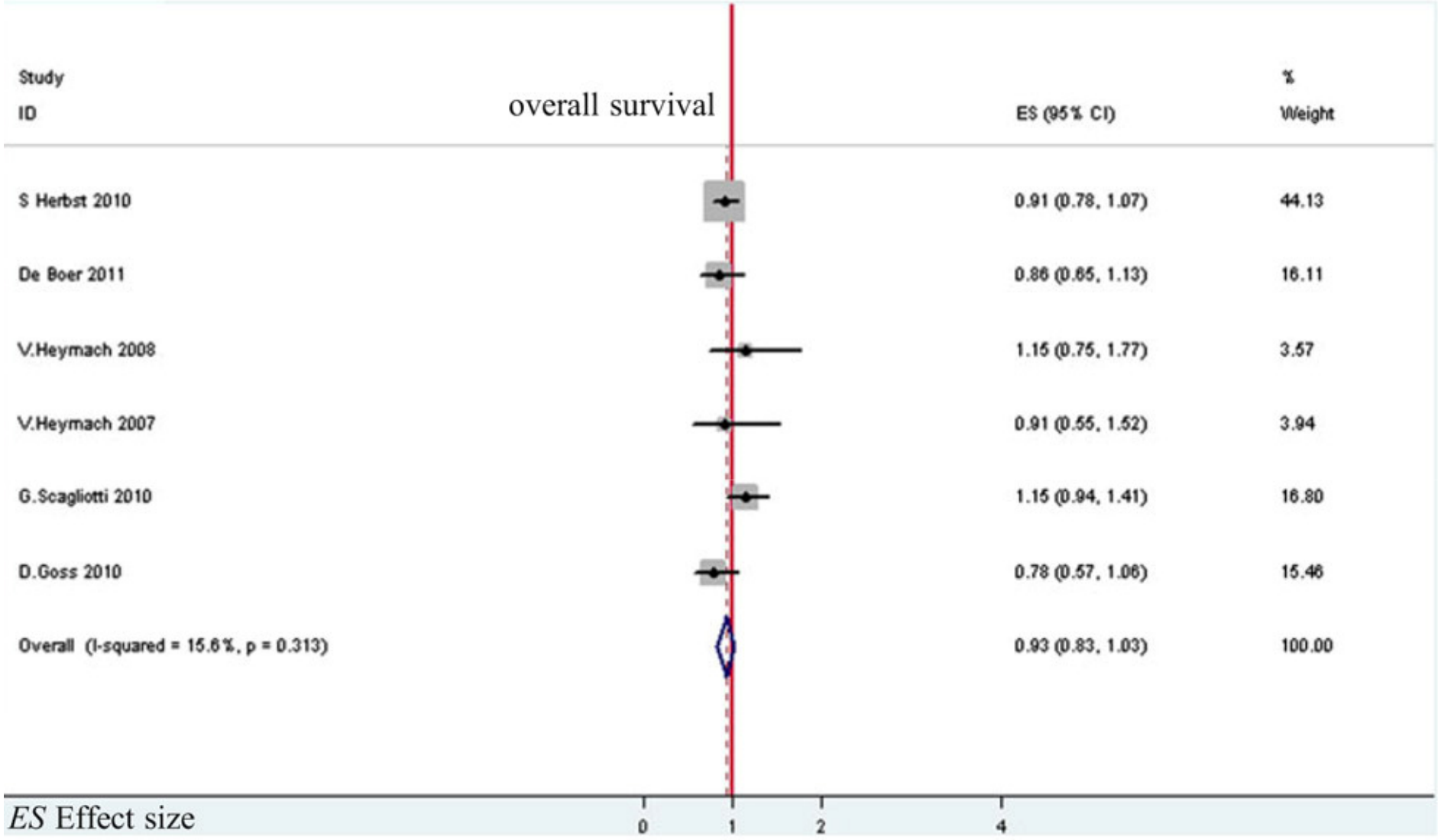
XIAO et al., 2012

patients with advanced non-small-cell lung cancer (NSCLC)

chemotherapy plus multitargeted antiangiogenic tyrosine kinase inhibitors (TKI)



XIAO et al., 2012



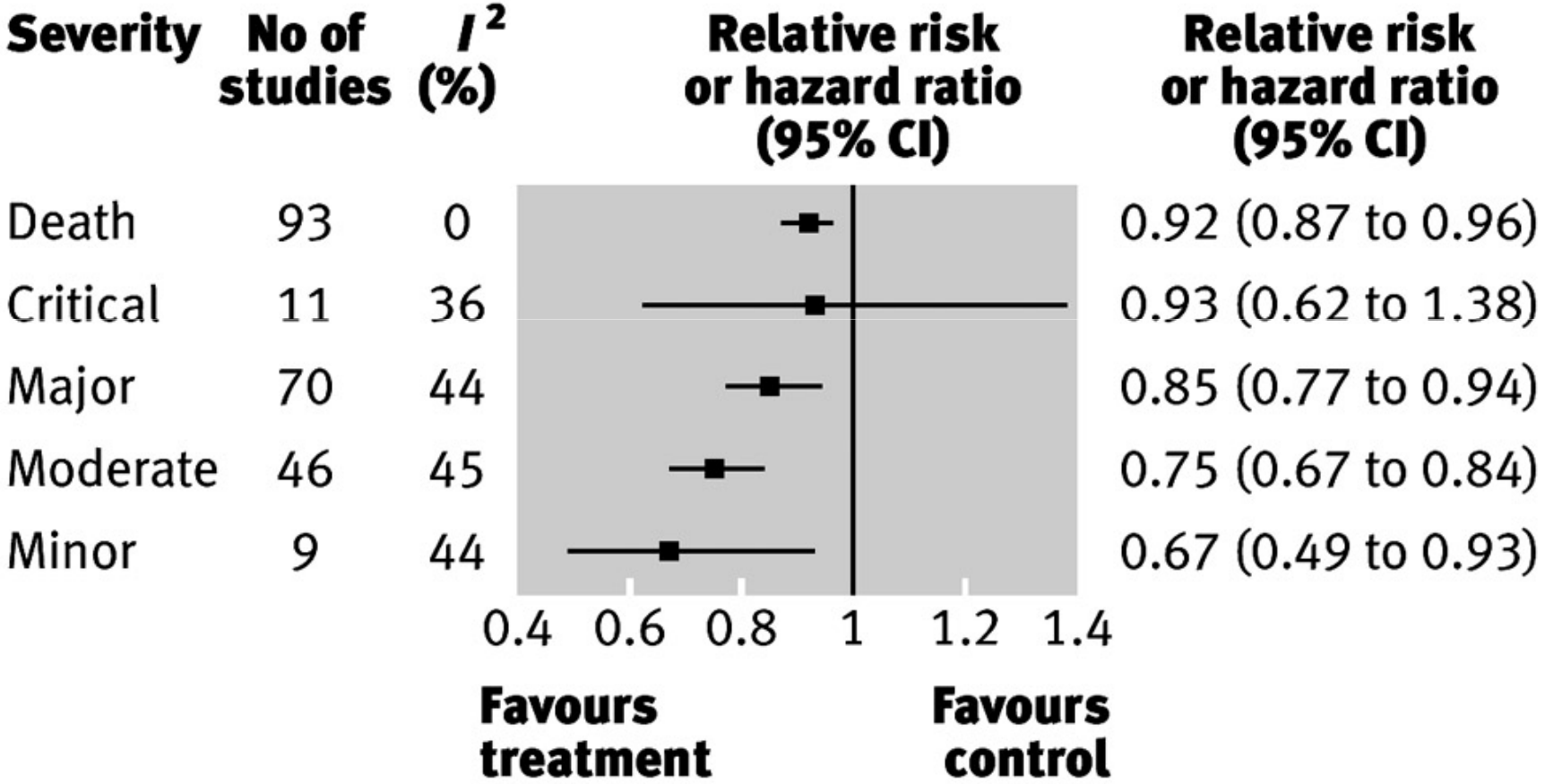
XIAO et al., 2012

EVIDENCE

- INAPPROPRIATE USE OF PLACEBO
- DESIGN OF NON INFERIORITY
- SURROGATE END-POINTS
- COMPOSITE END-POINTS

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

COMPOSITE END-POINTS



Ferreira-Gonzàlez et al., 2007

RCT and “REAL LIFE” PATIENTS

Participation of Females in Phase I Trials by Product Type

Product type	No. (%) of Studies That Include Female Participants	No. (%) of Participants That Are Female
Anesthesia, analgesia, and rheumatology	22 (88.0)	288 (33.8)
Antiviral	50 (74.6)	645 (27.5)
Cardio-renal	30 (54.5)	188 (27.8)
Gastroenterology	6 (60.0)	147 (43.8)
Metabolism and endocrinology	19 (65.5)	242 (36.4)
Neurology	12 (36.4)	306 (33.2)
Oncology	50 (76.9)	747 (34.2)
Psychiatry	19 (67.9)	234 (26.0)
Pulmonary and allergy	5 (41.7)	43 (24.9)
Reproductive and urologic	3 (100)	105 (37.2)
Special pathogen and transplant	16 (57.1)	148 (26.5)

Pinnow et al., 2009

How representative are clinical study patients with asthma or COPD for a larger “real life” population of patients with obstructive lung disease?

Kjetil Herlanda, Jan-Petter Akselsenb, Ole Henning Skjønsbergc, Leif Bjermerd

We conclude that “evidence based” treatment decisions for OLD are based on studies which include a very small and highly selected fraction of this patient population. It is questionable whether such data can extrapolated to a larger, “real life” population of patients with obstructive lung disease.

Respiratory Medicine (2005) 99, 11-19

Quality of randomised trials in COPD.

Bausch B1, Spaar A, Kleijnen J, Puhan MA.

257 trials assessed pharmacological.
The generation of appropriate randomisation was reported in 27.0% of the trials, concealment of random allocation in 11.6% and an intention-to-treat analysis in 21.8% of trials.

Eur Respir J. 2009 Nov;34(5):1060-5

EVIDENCE

- INAPPROPRIATE USE OF PLACEBO
- DESIGN OF NON INFERIORITY
- SURROGATE END-POINTS
- COMPOSITE END-POINTS
- UNDER EVALUATION OF ADVERSE REACTIONS

REAZIONI AVVERSE DA FARMACI ANTIASMATICI NEI BAMBINI

- MOLTI STUDI CLINICI POCHI RAPPORTI SU REAZIONI AVVERSE
- I PAZIENTI INCLUSI SONO MASCHI (6-11 ANNI)
- PIÙ RAPPORTI SU FARMACI POCO UTILIZZATI
- POCHE INFORMAZIONI SUI MOLTI PAZIENTI CHE ABBANDONANO GLI STUDI

Aagaard, Hansen, 2014

3 KEYWORDS

- EVIDENCE
- ETHICS

METHODOLOGICAL REQUIREMENTS FOR CLINICAL TRIALS

Ask important questions…

…answer them reliably

The objective is the patient,

the goal is his benefit

Yusuf S, Collins R, Peto R.
Why do we need some large, simple randomized trials? Stat Med 1984; 3: 409-420

ETHICS

- PARTICIPATION TO PROTOCOL PREPARATION

ETHICS

- PARTICIPATION TO PROTOCOL PREPARATION
- REGISTRATION OF THE PROTOCOL

ETHICS

- PARTICIPATION TO PROTOCOL PREPARATION
- REGISTRATION OF THE PROTOCOL
- INFORMED CONSENT

ETHICS

- PARTICIPATION TO PROTOCOL PREPARATION
- REGISTRATION OF THE PROTOCOL
- INFORMED CONSENT
- PROPERTY OF DATA

ETHICS

- PARTICIPATION TO PROTOCOL PREPARATION
- REGISTRATION OF THE PROTOCOL
- INFORMED CONSENT
- PROPERTY OF DATA
- ACCESS TO RAW DATA

ETHICS

- PARTICIPATION TO PROTOCOL PREPARATION
- REGISTRATION OF THE PROTOCOL
- INFORMED CONSENT
- PROPERTY OF DATA
- ACCESS TO RAW DATA
- PUBLICATION INDEPENDENTLY FROM RESULTS

Non-publication was more common among trials that received industry funding (150/468, 32%) than those that did not (21/117, 18%), P=0.003. Of the 171 unpublished trials, 133 (28%) had no results available in ClinicalTrials.gov.

Non-publication of large randomized clinical trials: cross sectional analysis

Christopher W Jones attending physician, Lara Handler school of medicine liaison librarian, Karen E Crowell clinical information specialist2, Lukas G Keil research assistant, Mark A Weaver assistant professor, Timothy F Platts-Mills assistant professor

Of 585 registered trials, 171 (29%) remained unpublished.

These 171 unpublished trials had an estimated total enrollment of 299 763 study participants. The median time between study completion and the final literature search was 60 months for unpublished trials.

BMJ 2013;347:f6104 doi:

3 KEYWORDS

- EVIDENCE
- ETHICS
- LEGISLATION

Regulatory confidentiality

The reasons for transparency

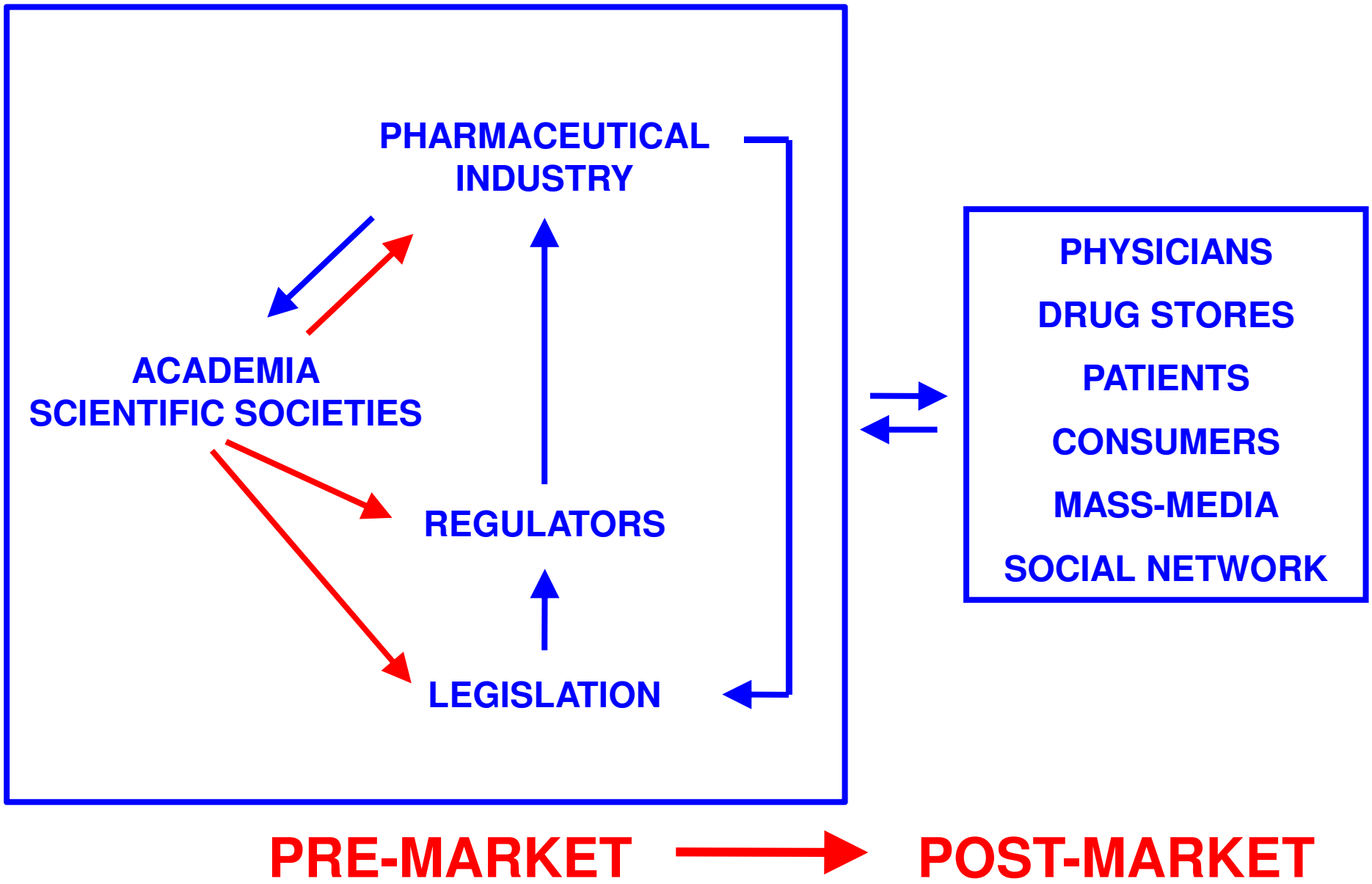
- The industry is not the sole financer of research.
- Clinical trials require the participation of patients, who take part free of charge.
- In most European states the drug market is prosperous because it is guaranteed by national health services.
- Secrecy may be justifiable in connection with information regarding the production of the active principles and the methods utilized for drug discovery.
- But information on drug development including pre-clinical findings and clinical controlled trials must be available for scrutiny by clinicians and patients.

CHANGE NEEDED IN EUROPEAN LEGISLATION

- QUALITY, EFFICACY, SAFETY
- QUALITY, EFFICACY, SAFETY AND THERAPEUTIC ADDED VALUE

Two pivotal trials needed to support MAA

One sponsor-driven RCT	One independent RCT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