

# NON-INFERIORITY TRIALS



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# METHODOLOGICAL REQUIREMENTS FOR CLINICAL TRIALS

Ask important questions...

...answer them reliably

The objective is the patient,

the goal is his benefit

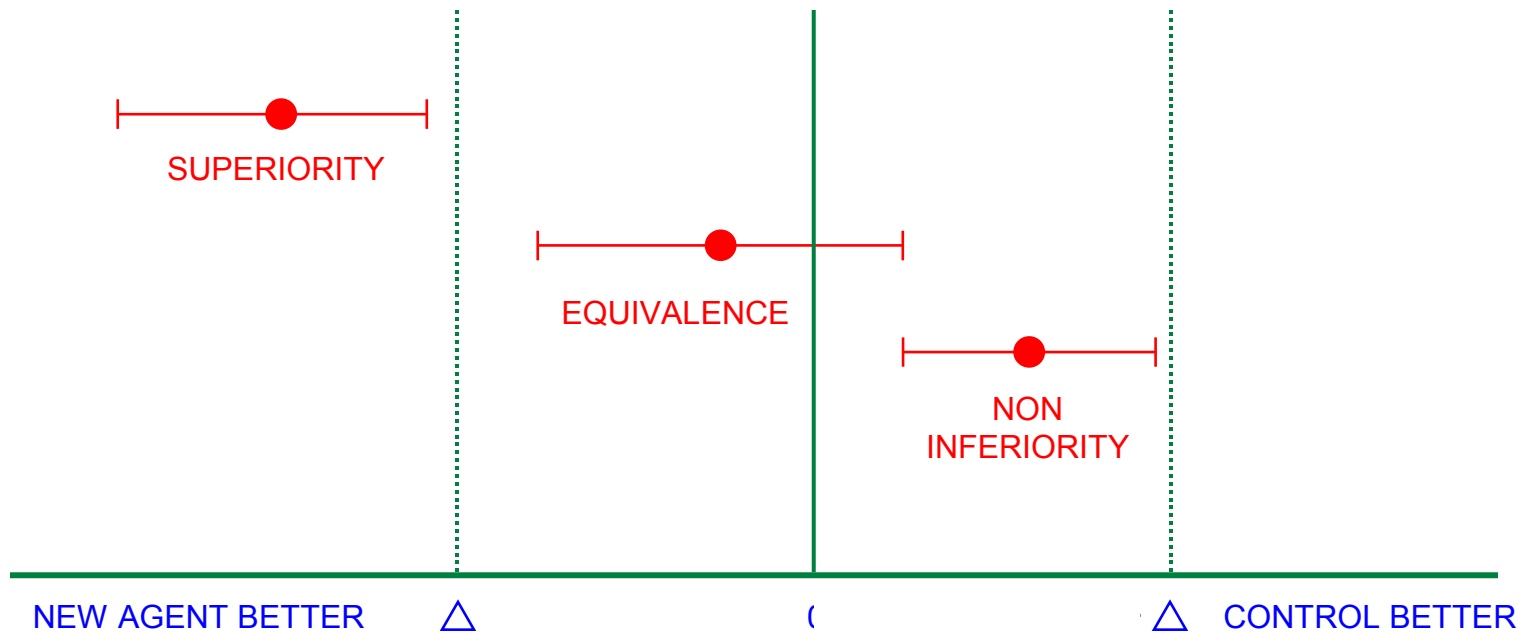
*Yusuf S, Collins R, Peto R.*

*Why do we need some large, simple randomized trials? Stat Med 1984; 3: 409-420*

# OBJECTIVES OF STUDIES WITH DRUGS

- EFFICACY FOR A DISEASE WITHOUT THERAPY
- SUPERIORITY OF EFFICACY
- INFERIORITY OF ADVERSE REACTIONS
- ACTIVITY ON PATIENTS RESISTANT TO TREATMENT WITH OTHER DRUGS
- BETTER COMPLIANCE RESULTING IN A BETTER OUTCOME

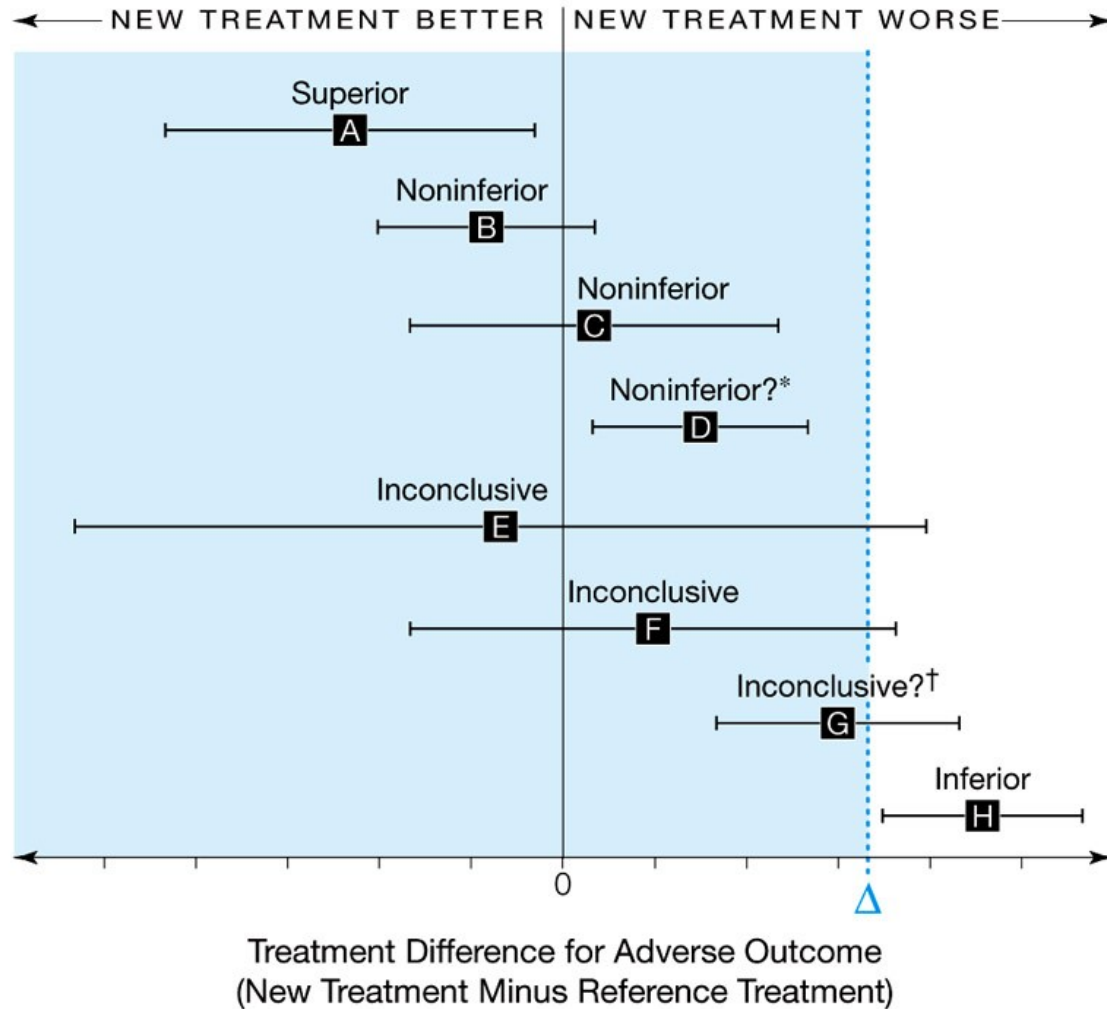
PATIENTS CAN BE INVOLVED IN CLINICAL TRIALS ONLY IF THERE IS A REASONABLE POTENTIAL ADVANTAGE. FOR THEM OR FOR FUTURE PATIENTS THE ADVANTAGE COULD BE INCREASED EFFICACY, DECREASED TOXICITY, DIFFERENT TOXIC PROFILES, BETTER COMPLIANCE. LONGER DURATION OF ACTION, etc.



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

# Possible Scenarios of Observed Treatment Differences in Non-inferiority Trials



TRIALS (ANNI)	DESIGN	
	EQUIVALENCE NON-INFERIORITY	
1900-1994	3	1*
1995-1999	9	2
2000-2004	42	14
2005-2008 (August)	72	24
	126	41

Randomized clinical trials, English language, pubmed

\* Pubmed “core Journals”

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- Testing non-inferior efficacy for the sake of better safety.  
**This is reasonable if the outcome events measuring efficacy and safety have comparable clinical importance as, for instance, deaths and devastating hemorrhagic strokes after thrombolysis in AMI. In these circumstances, however, a superiority trial would compare the effectiveness of two treatments better in terms of survival without strokes by cumulatively measuring efficacy and safety events.**

AS A JUSTIFICATION OF NON-INFERIORITY TRIALS  
IT IS FREQUENTLY SAID THAT CLINICIANS NEED  
DRUGS WITH LESS SIDE-EFFECTS. IT IS HOWEVER  
FORGOTTEN THAT THIS ADVANTAGE CAN HARDLY  
BE ESTABLISHED IN A NON-INFERIORITY TRIAL.  
IF THERE IS CLINICAL ADVANTAGE IN DRUG  
SIDE-EFFECT THIS SHOULD RESULT IN A BETTER  
OUTCOME.

# EQUIVALENCE/NON INFERIORITY TRIALS

How to establish the limits (excess of outcome events) that define a drug as equivalent/not inferior?

Is a 10%, 5% or even 2% difference (possibly in mortality) acceptable as equivalent in the interest of patients?

CONSTANCY ASSUMPTION IS THE PRINCIPAL  
OBSTACLE TO MEANINGFUL N.I. TRIALS

DIFFICULTY TO REPRODUCE THE CONDITIONS  
WHERE THE COMPARATOR HAS BEEN FOUND  
BETTER THAN PLACEBO.

# **Efficacy and safety of etoricoxib 30 mg and celecoxib 200 mg in the treatment of osteoarthritis in two identically designed, randomized, placebo-controlled, non-inferiority studies**

C. O. Bingham, III, A. I. Sebba<sup>1</sup>, B. R. Rubin<sup>2</sup>, G. E. Ruoff<sup>3</sup>, J. Kremer<sup>4</sup>, S. Bird<sup>5</sup>, S. S. Smugar<sup>5</sup>, B. J. Fitzgerald<sup>5</sup>, K. O'Brien<sup>5</sup> and A. M. Tershakovec<sup>5</sup>

**Conclusions.** Etoricoxib 30 mg qd was at least as effective as celecoxib 200 mg qd and had similar safety in the treatment of knee and hip OA; both were superior to placebo.

Johns Hopkins University, Baltimore, MD, <sup>1</sup>Arthritis Associates, Palm Harbor, FL, <sup>2</sup>University of North Texas, Fort Worth, TX, <sup>3</sup>Westside Family Medical Centre, Kalamazoo, MI, <sup>4</sup>The Centre for Rheumatology, Albany, NY and <sup>5</sup>Merck & Co., Inc., West Point, PA, USA.

Rheumatology 2007 46(3):496-507

# VARIABILITY IN TWO IDENTICAL NON-INFERIORITY RCT

PLACEBO	STUDY 1	STUDY 2
ANY ADVERSE REACTIONS	42 (33.1%)	61 (52.1%)
DRUG RELATED AR	7 (5.5%)	20 (17.1%)
SERIOUS AR	3 (2.4%)	5 (4.3%)

Brigham III et al., 2007

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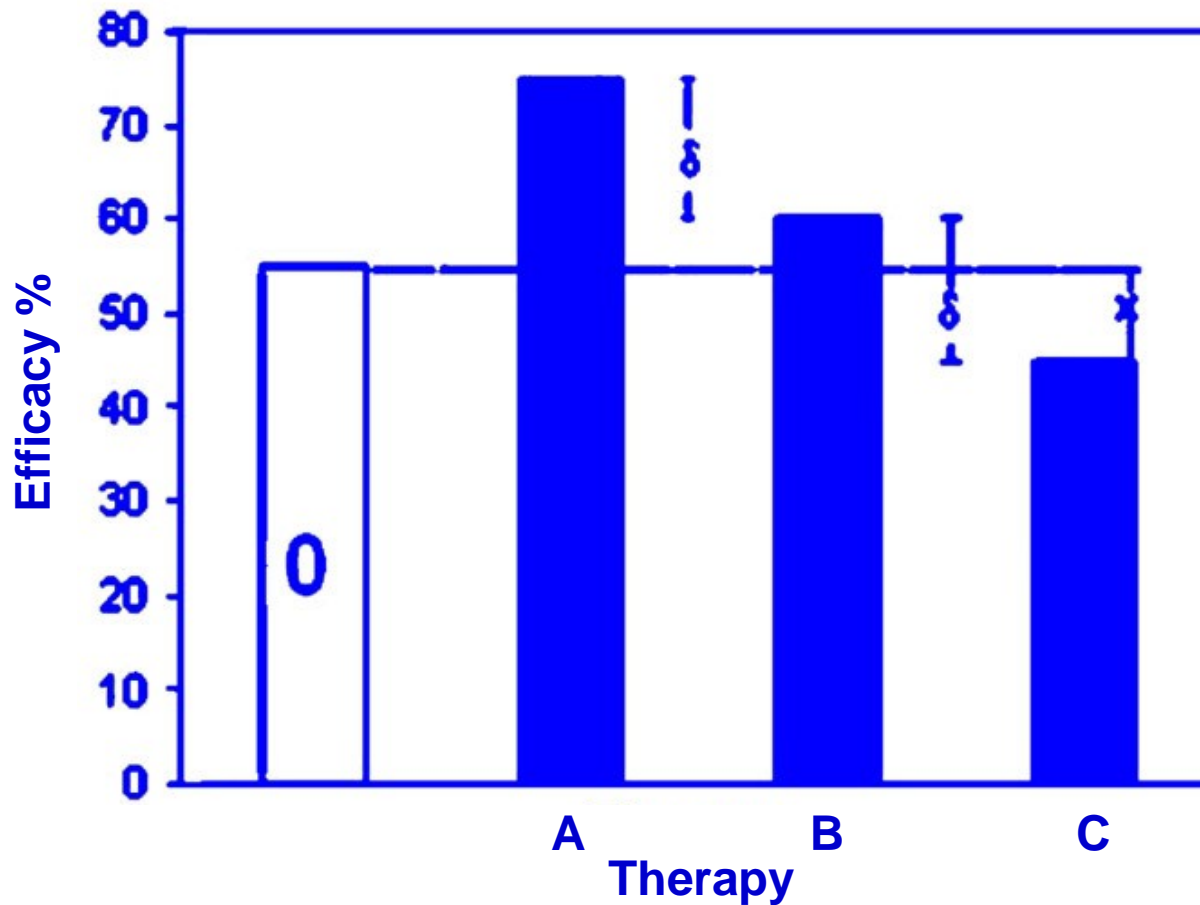
DIFFERENCE ETORICOXIB-CELECOXIB	STUDY 1	STUDY 2
ANY ADVERSE REACTIONS	- 3.8%	+ 3.3%
DRUG RELATED AR	- 0.8 %	+ 4.7 %
SERIOUS AR	- 2.2 %	- 0.8 %

Brigham III et al., 2007

DEVIATIONS FROM INCLUSION CRITERIA OR FROM THE SCHEDULE, ADMINISTRATION OF WRONG TREATMENT OR PATIENT NON-ADHERENCE TO TREATMENT ARE FACTORS THAT MAKE A CONCLUSION OF NO DIFFERENCE MORE LIKELY IN NON-INFERIORITY TRIALS. THE OPPOSITE MIGHT BE TRUE FOR SUPERIORITY TRIALS.

SPLAWINSKI and KUZNIAR  
SCIENCE AND ENGINEERING ETHICS 2004,10,73

USING N.I. TRIALS TO EVALUATE INTERVENTIONS  
NOT EXPECTED TO PROVIDE IMPORTANT  
EFFICACY OR SAFETY ADVANTAGE OVER STD  
INTRODUCES SUBSTANTIAL RISKS OF ERODING  
THE PROGRESS MADE IN BENEFITS DELIVERED  
BY CURRENT THERAPIES...



Biocreep in a non-inferiority trial. *A* = Standard surgical procedure (efficacy of 75%), originally superior to initial procedure (0, efficacy of 55%). *B* = New therapy (efficacy 60%) non-inferior compared to *A* with a delta less than 20%. Another therapy *C* (efficacy 45%) non-inferior to therapy *B* with a delta less than 20%. Erroneous conclusion that  $C = B = A$ , which is superior to 0. In fact, the efficacy of therapy *C* is worse than 0 by a difference  $x$ .

# QUALITY OF NON-INFERIORITY OR EQUIVALENCE TRIALS

- 1/3 OMISSION OF SAMPLE SIZE CALCULATION
- 1/3 CONFIDENCE INTERVALS INCONSISTENT
- 1/2 ERRONEOUS STATISTICAL TESTS
- 4% OF TRIALS GAVE A JUSTIFICATION FOR THE MARGIN USED

Le Henannf et al., JAMA 2006, 295, 1147

## OUT OF 383 CLINICAL TRIALS

64 % COULD DETECT A DIFFERENCE > 50 %

84 % COULD DETECT A DIFFERENCE > 25 %

MOHER et al., 1994

THE USE OF NON-INFERIORITY TRIALS  
IMPLIES THE REFUSAL OF THE CONCEPT  
THAT A NEW DRUG MUST SHOW AN  
ADDED VALUE

A DRUG APPROVED WITH A NON-INFERIORITY TRIAL MAY LATER BECOME A STANDARD AND MAY NOT BE TESTED AGAIN FOR “ETHICAL REASONS”.

ANY NEW DRUG CARRIES POSSIBLE  
RISKS. IT IS UNETHICAL TO RECRUITE  
PATIENTS FOR A TRIAL WITHOUT  
PROSPECTIVES OF SOME BENEFIT

A DEMONSTRATION OF NON INFERIORITY LEAVES  
THE PRODUCT IN A KIND OF LIMBO: ITS PLACE IN  
THERAPY IS NOT ESTABLISHED, ALTHOUGH ITS  
PLACE ON THE MARKET IS ASSURED

WHO WILL ACCEPT CONDITIONS WHERE  
1% MORE DEATHS OR INFARCTIONS OR  
STROKES ARE CONSIDERED NON-INFERIOR?



Garattini S, Bertele V.  
How can research ethics committees protect patients better?  
BMJ 2003; 326:1199-201

## Draft informed consent

“Let us treat you with something that at best is the same as what you would have had before, but might also reduce - though this is unlikely - most of the advantages previously attained in your condition. It might even benefit you more than any current therapy but, should that actually happen, we shall not be able to prove it. Nor have we enough chance to let you know whether the new treatment may somehow bother or even harm you more than the standard one”.

## NON-INFERIORITY TRIALS

FEW PATIENTS WOULD AGREE TO  
PARTICIPATE IF THIS MESSAGE IS  
CLEAR IN THE INFORMED CONSENT FORM.

A new US FDA draft guideline formally rejects the use of non-inferiority studies in the development of antimicrobial drugs for acute bacterial exacerbations of chronic bronchitis (ABECB), making clear that only superiority trials are recommended.

Scrip 12/09/08

# EMA GUIDELINES ON ALZHEIMER'S AND PARKINSON'S TRIALS

NON-INFERIORITY TRIALS WILL NOT BE ACCEPTED  
AS PROOF OF EFFICACY. INSTEAD, THERAPIES  
MUST DEMONSTRATE SUPERIORITY AGAINST  
ACTIVE CONTROLS\* AND AGAINST PLACEBO

\*a cholinesterase inhibitor for Alzheimer's disease; a dopamine agonist or precursor for Parkinson's disease