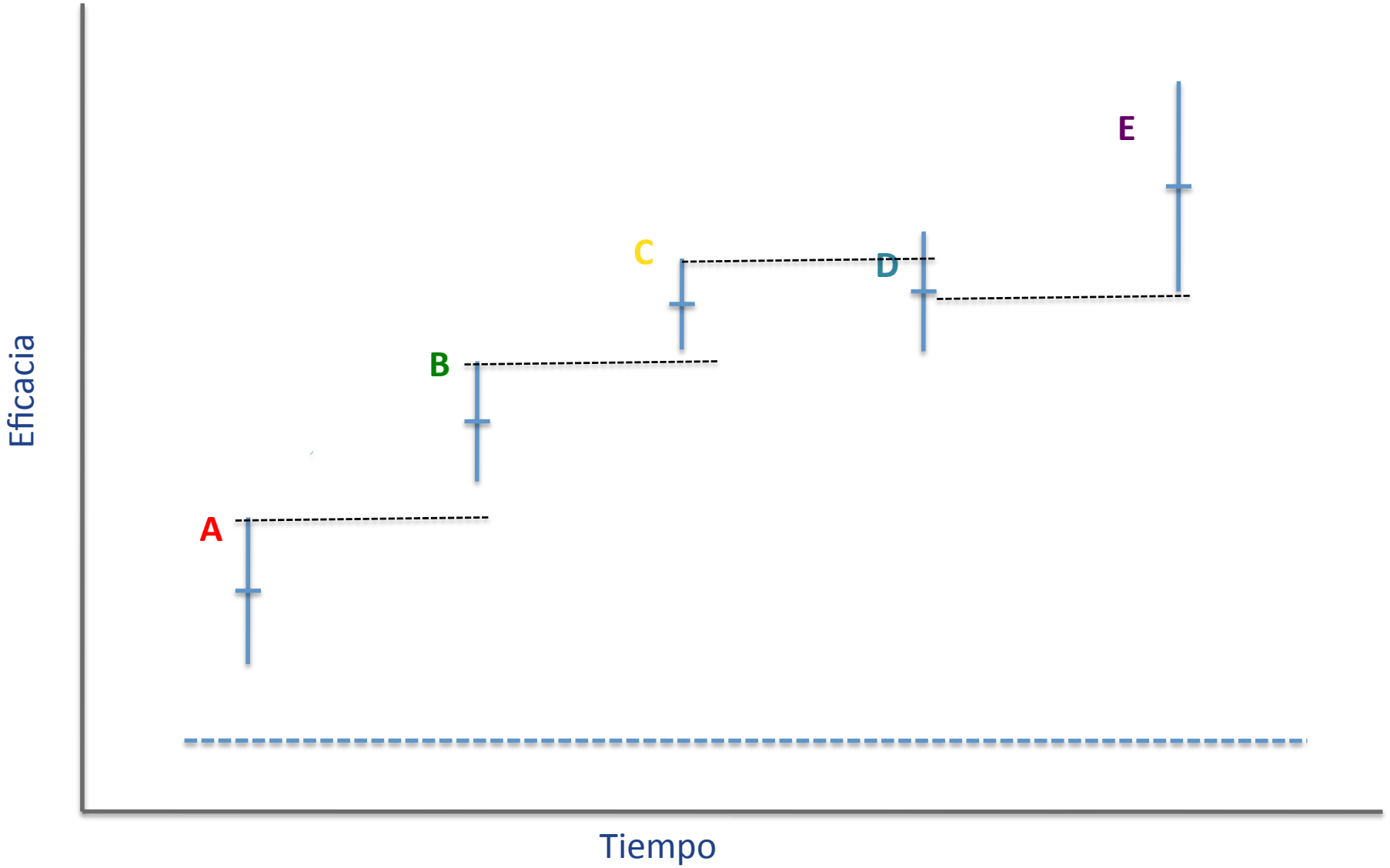
Un cuento de superioridad, equivalencia y no inferioridad

Olga Delgado
Hospital Son Espases
Palma

Palma, jueves 10 mayo 2012
30 minutos

de la superioridad a la no-inferioridad



¿por qué se realizan estudios no-inferioridad?

- Éticas
- Mayor seguridad
- Mayor comodidad
- Eficacia difícil superar
- Tratamientos alternativos o segundas líneas
- Conocer la eficacia comparada

el mundo al revés

Schumi J and Wittes T. Throug the looking glass; understanding non-inferioty. Trials 2011; 12: 106

¿cómo se plantean los ensayos?

	HIPÓTESIS NULA H(o)	HIPÓTESIS ALTERNATIVA H(a)
SUPERIORIDAD	C=E Son iguales	E≠C **Son diferentes**

	HIPÓTESIS "ya no tan" NULA H(o)	HIPÓTESIS ALTERNATIVA H(a)
EQUIVALENCIA	C ≠ E Son diferentes	C≈E **Son equivalentes**

	HIPÓTESIS "tampoco" NULA H(o)	HIPÓTESIS ALTERNATIVA H(a)
NO-INFERIORIDAD	C - E ≥ M La diferencia es mayor de lo aceptado	C - E < M **La diferencia está en el margen de NI**

Dunnett CW, Gent M. Biometrics 1977; 33: 593-602.

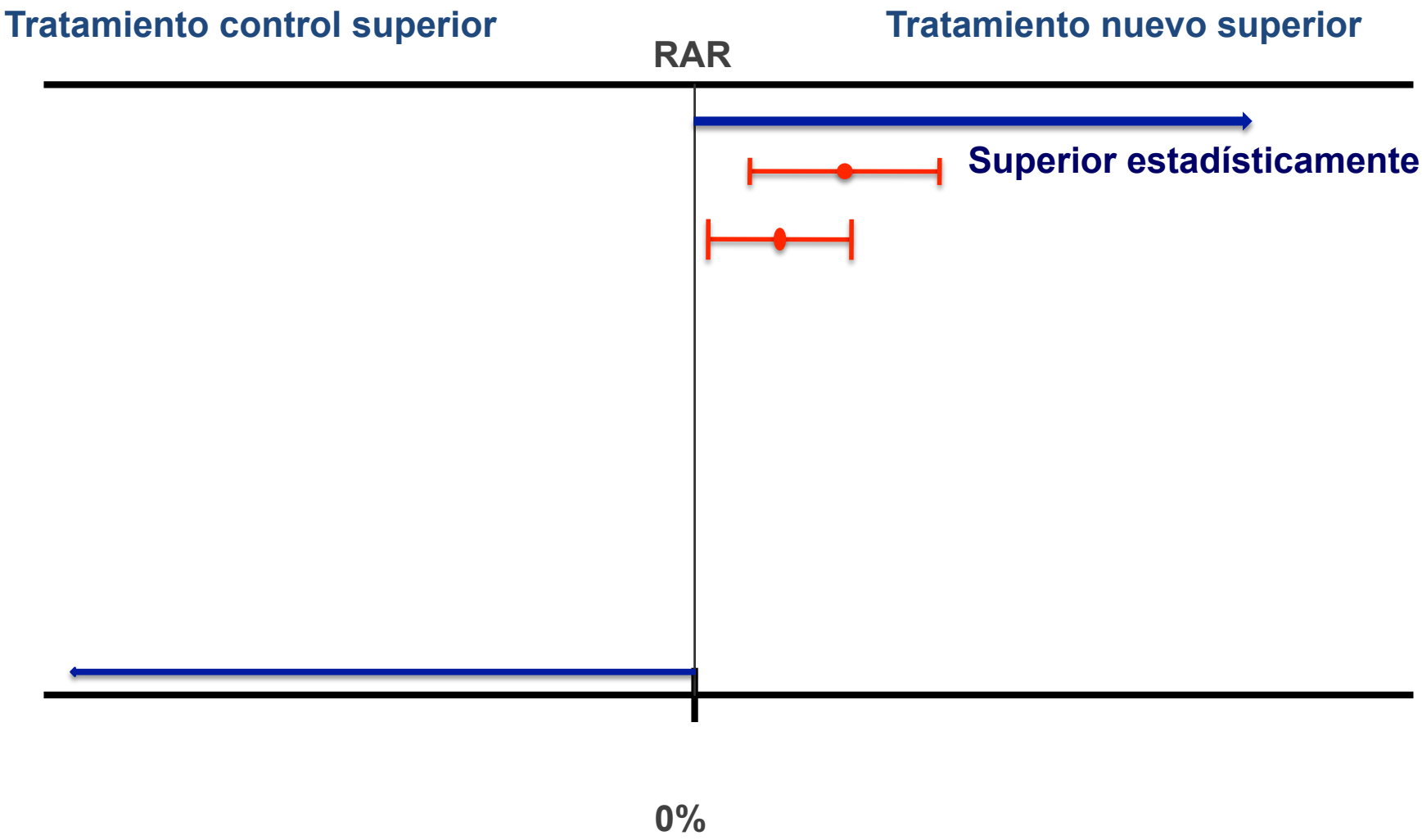
Blackwelder WC. Control Clin Trials 1982; 3: 345-53.

La hipótesis “no nula” es solo la primera sorpresa de Alicia

esto no ha hecho
más que empezar…

Schumi J and Wittes T. Throug the looking glass; understanding non-inferioty. Trials 2011; 12: 106

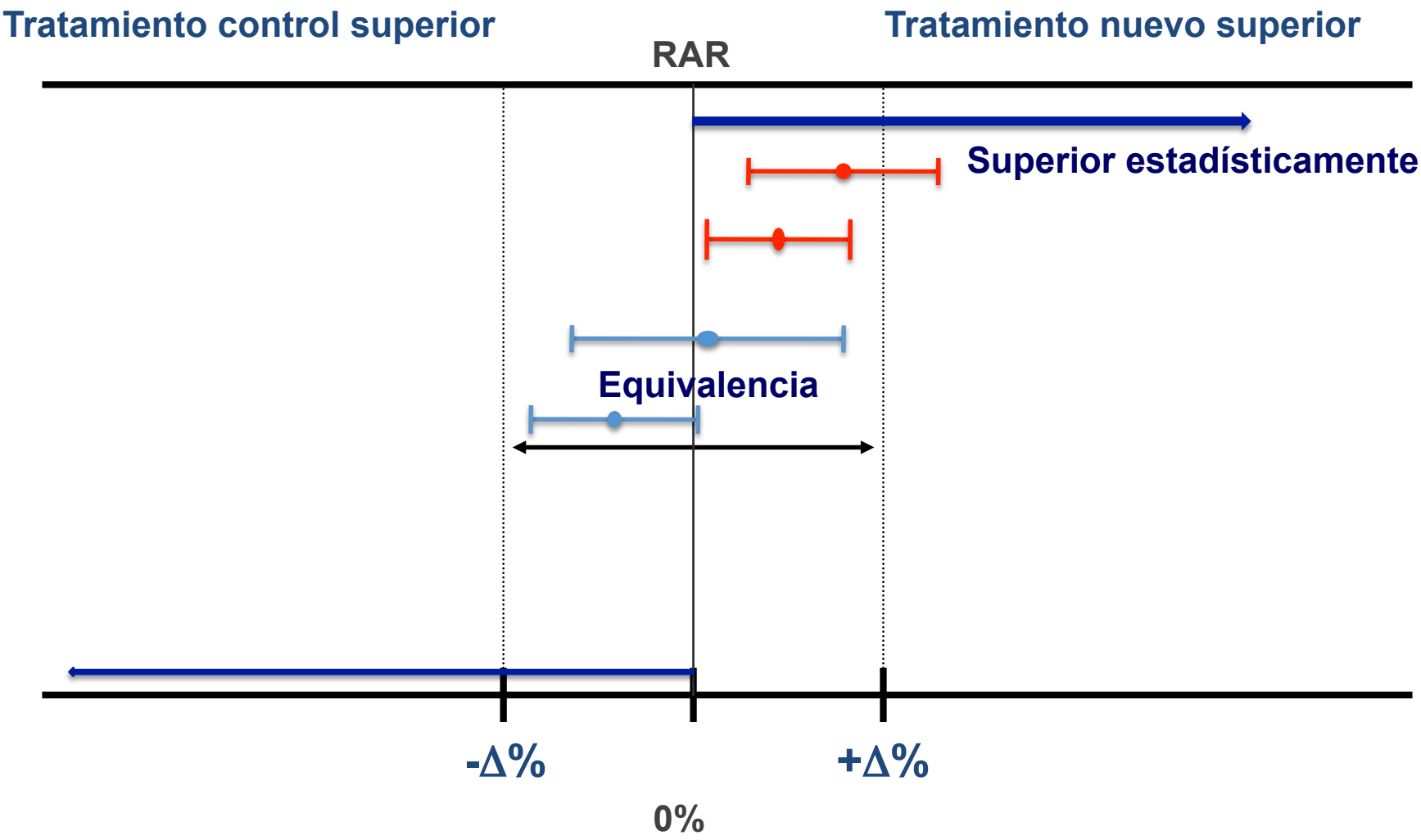
Comparación gráfica de tipos de estudios



Equivalencia terapéutica

La diferencia entre los tratamientos está dentro de un margen preestablecido que se considera clínicamente irrelevante.

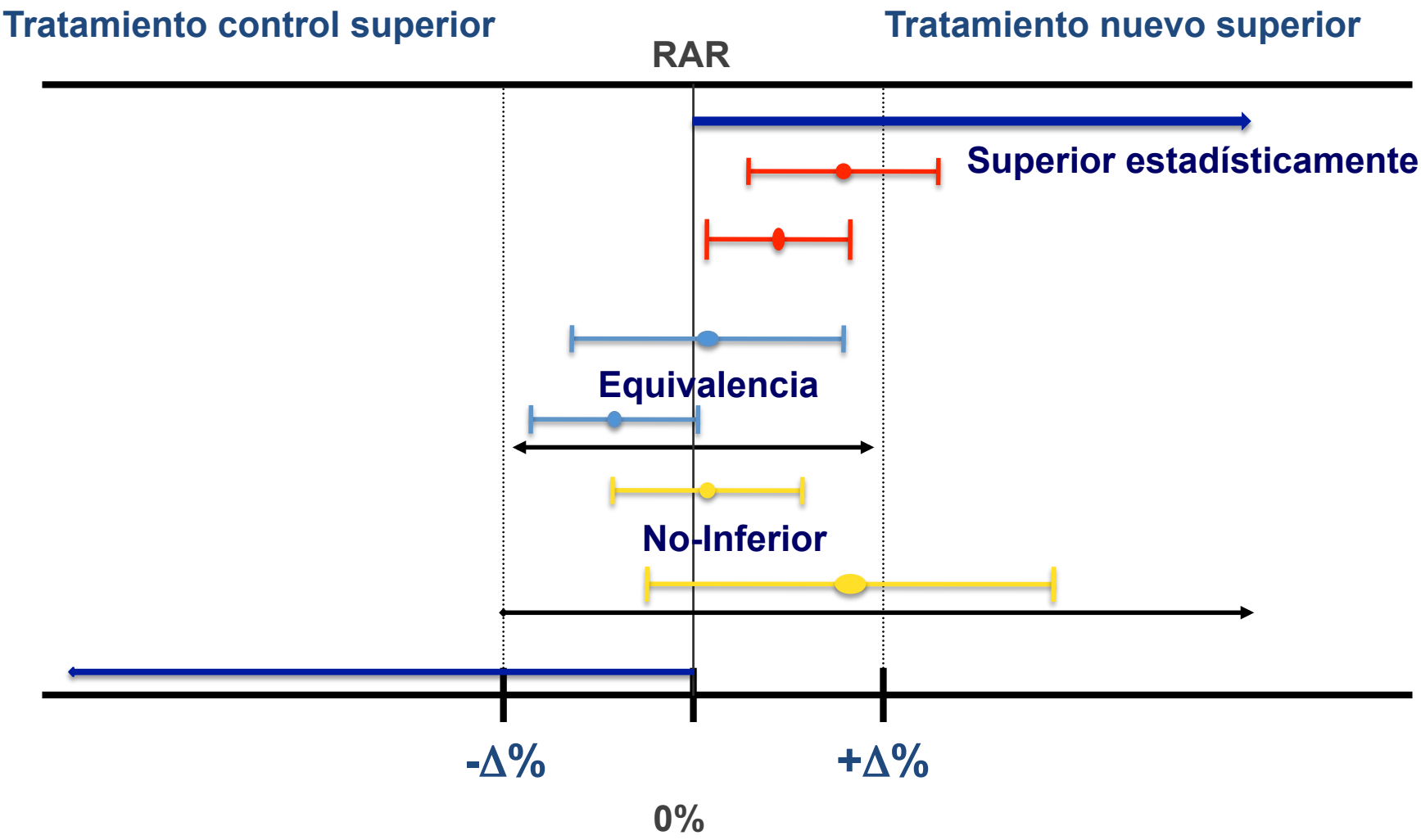
Comparación gráfica de tipos de estudios



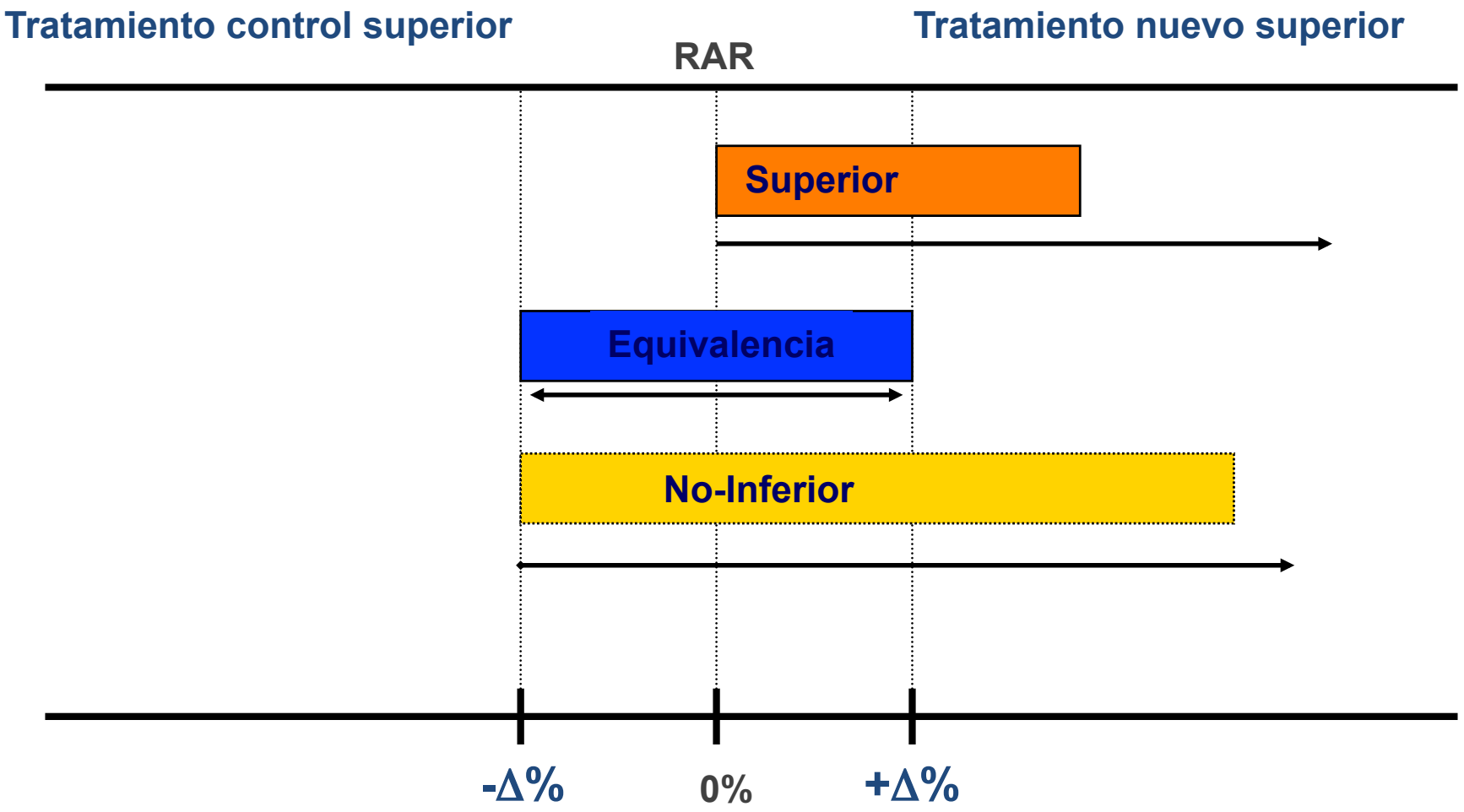
No inferioridad

La nueva intervención no es peor que el control, o mejor dicho, no es “inaceptablemente” peor que el control.

Comparación gráfica de tipos de estudios



Comparación gráfica de tipos de estudios



3. Study Design Options

- Superiority trial designs

Phase-3 superiority trials can include *add-on* or *substitution* comparisons. In the first case, the investigational drug plus a standard combination regimen is compared to placebo plus the same standard regimen. In some cases, an experimental drug could be added to a background regimen of drugs that the participant or investigator chooses from a list of possibilities.

For substitution comparisons, the investigational drug is substituted for a component of a standard regimen. This regimen is then compared to the standard regimen.

- Noninferiority trial designs

Noninferiority trials use substitution comparisons as described above. For noninferiority comparisons, it is important that the contribution of the substituted drug to a regimen's overall activity be previously characterized in the population of interest. This is often referred to as a study's *assay sensitivity*. This information should be used to support a noninferiority comparison and to calculate an appropriate sample size. This will be discussed further under section III. C. 3., Choice of Control Arms.

US Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research. Guidance for industry: antiretroviral drugs using plasma HIV RNA measurements -- clinical considerations for accelerated and traditional approval. http://www.fda.gov/CDER/GUIDANCE/3647fnl.pdf (accessed May 1, 2008).

Objetivo

ORIGINAL ARTICLE

N ENGL J MED 364;5 NEJM.ORG FEBRUARY 3, 2011

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

STATISTICAL ANALYSIS

The trial was designed as a noninferiority study. A one-side lower 97,5% confidence interval was used in the analysis of the primary end point, the rate of clinical cure, with a noninteriority margin of -10 percentage points. If the lower bounday of the confience limit war within the 10-percentage-point margin, clinical noninferiority was demostrated. The secondary end points of recurrence and overall cure, which

Efficacy and Safety of Tenofovir DF vs Stavudine in Combination Therapy in Antiretroviral-Naive Patients

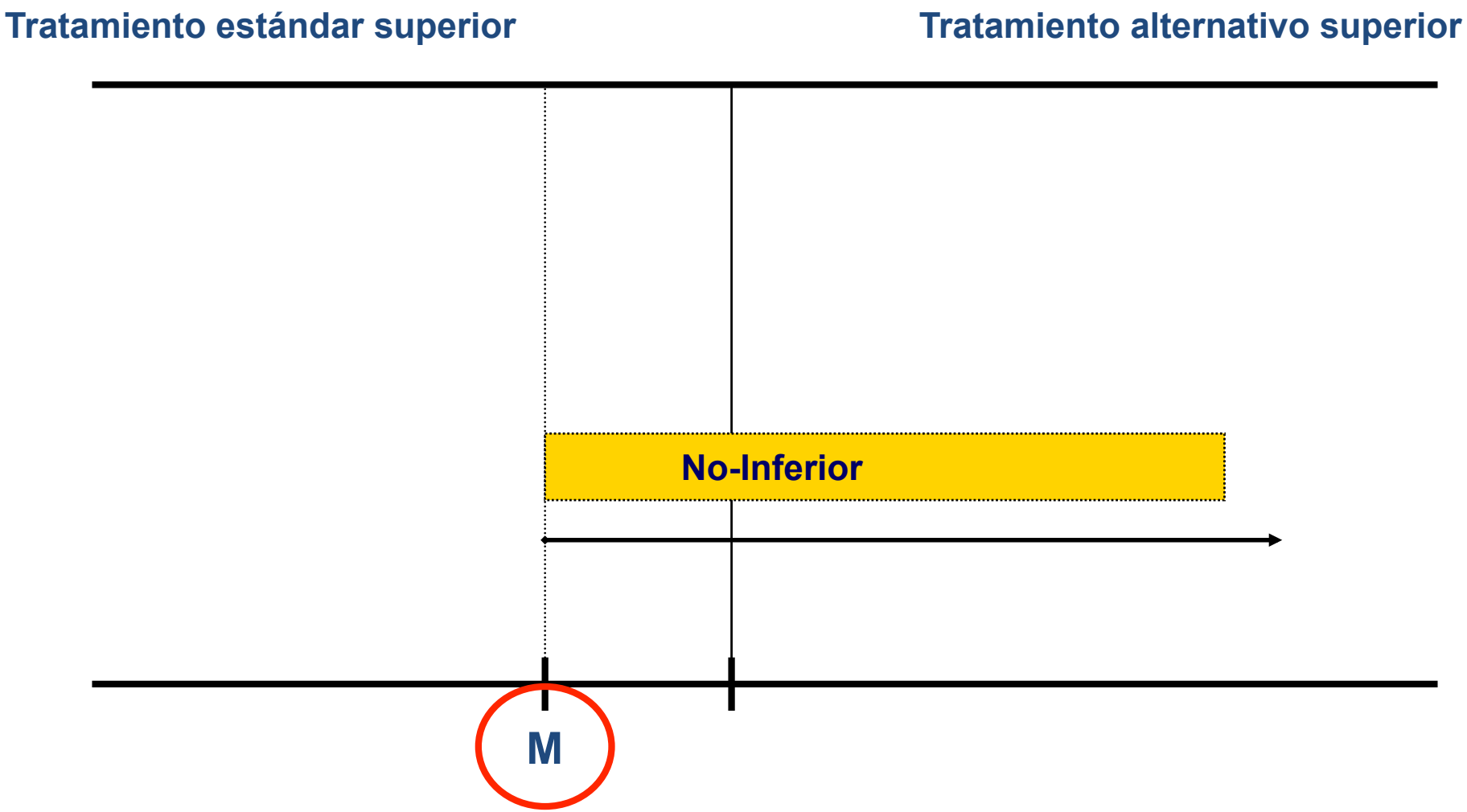
A 3-Year Randomized Trial

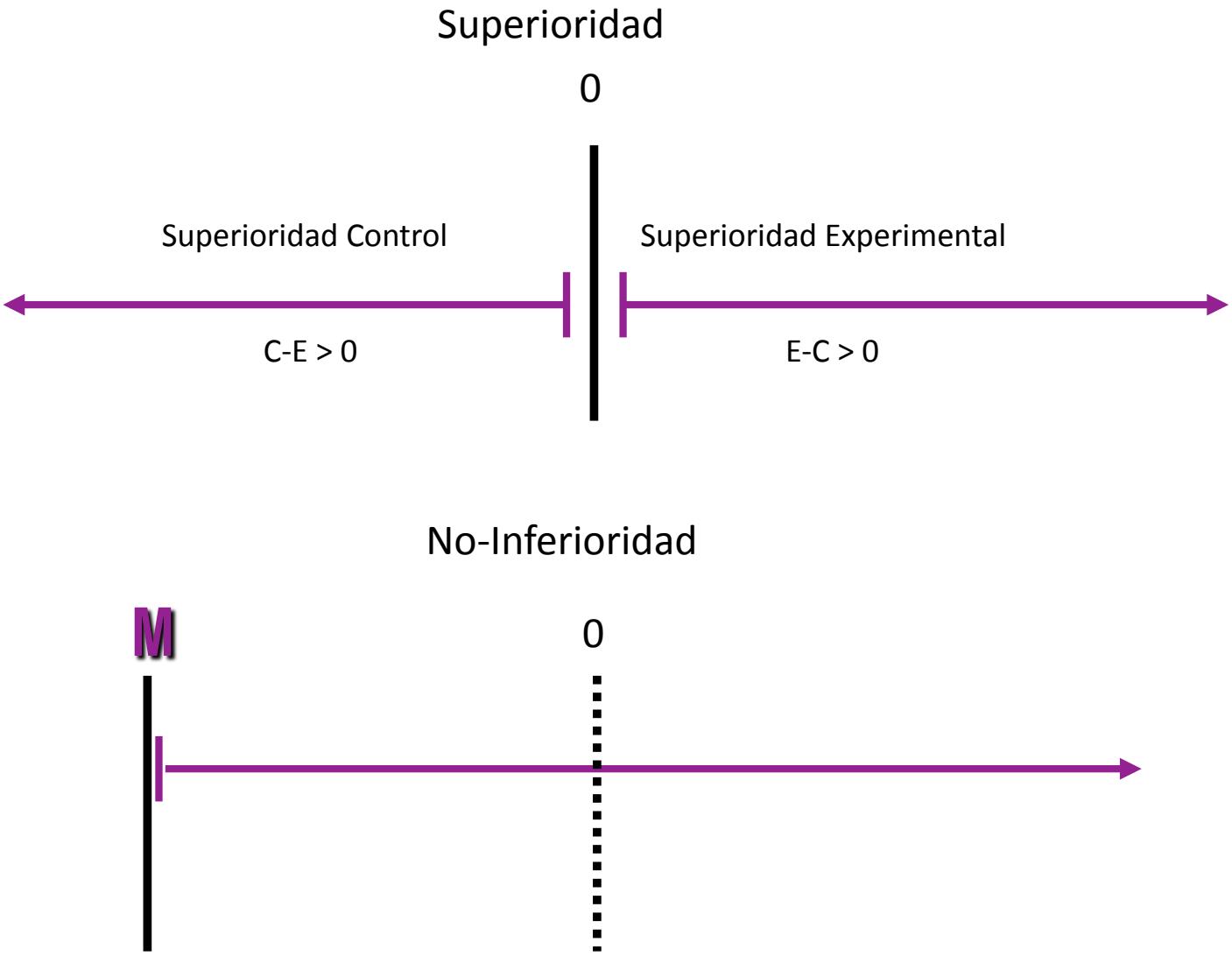
JAMA, July 14, 2004 (292)No.2

The primary objective of this study was to assess the equivalence of tenofovir DF vs stavudine in combination with lamivudine and efavirenz for the treatment of patients infected with HIV who were antiretroviral naive as determined by the proportion of patients in each regimen with plasma HIV RNA levels of less than 400 copies/mL. The sec-

There was no upper bound for the predefined CIs because the study was designed as a noninferiority trial (ie, equivalence) and the lower bound of the 2-sided 95% CI for the difference of the primary end point (the tenofovir DF group – stavudine group) was compared with −10% to determine noninferiority of tenofovir DF relative to stavudine.

Margen no-inferioridad




Superioridad
0
Superioridad Control
Superioridad Experimental
C-E > 0
E-C > 0
No-Inferioridad
M
0


I
NI

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 27 July 2005
Doc. Ref. EMEA/CPMP/EWP/215

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	December 1999 – January 2004
ADOPTION BY COMMITTEE FOR RELEASE FOR CONSULTATION	February 2004
END OF CONSULTATION (DEADLINE FOR COMMENTS)	May 2004
AGREED BY WORKING PARTY	June 2004
ADOPTION BY COMMITTEE	July 2005
DATE FOR COMING INTO EFFECT	January 2006

Guidance for Industry

Non-Inferiority Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Robert Temple at 301-796-2270 or Robert O'Neill at 301-796-1700 (CDER), or the Office of Communication, Outreach, and Development (CBER) at 301-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2010
Clinical/Medical

1. Oráculo del juicio clínico y la experiencia de pacientes:
   Preguntar a médicos y pacientes el grado de eficacia que estarían dispuestos a sacrificar por los beneficios de un nuevo tratamiento

2:25 – 2:40 p.m. BREAK

2:40 – 3:00 p.m. The perspective of industry: non-inferiority trials for CAP
Eddie Power

3:00 – 3:30 p.m. How to define an evidence-based non-inferiority margin with degrees of unavoidable uncertainty
Tom Fleming

Endpoints

Current knowledge of the "treatment effect" in clinical trials of outpatient pneumonia

10:50 – 11:20 a.m. What criteria should be addressed to do a credible non-inferiority trial and why is this clinically important?
Tom Fleming

11:20 – 11:35 a.m. Q&A Panel

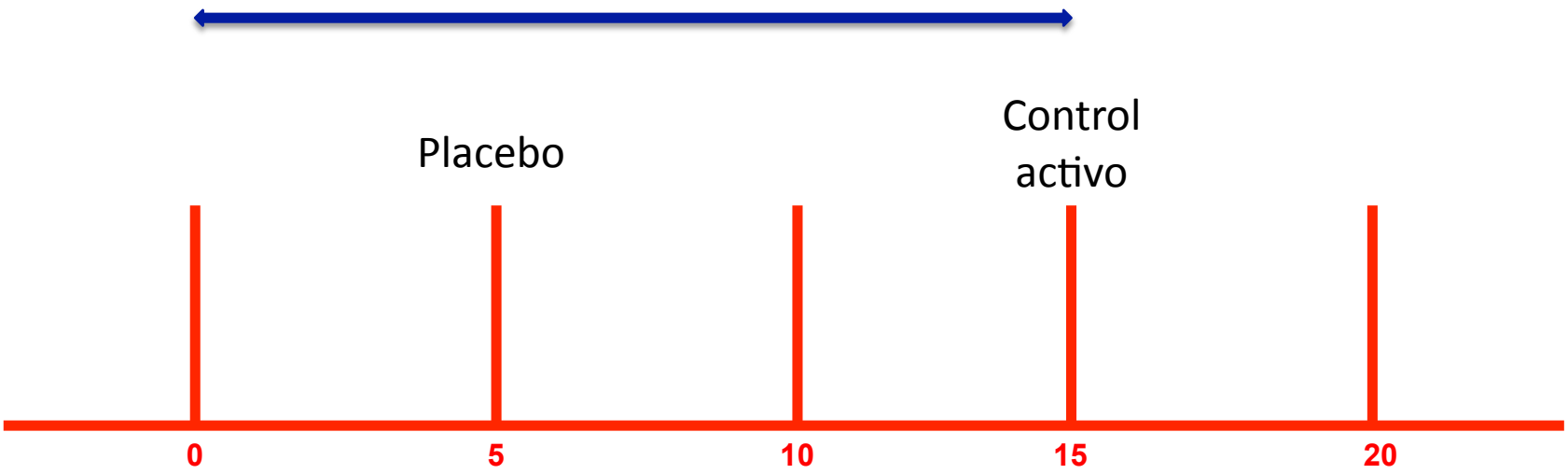
FDA. Public workshop cosponsored with IDSA: Clinical Trial Design for Community-Acquired Pneumonia. January 17, 2008. Crowne Plaza Hotel. Silver Spring.

2. Oráculo matemático o método Rothmann o 95%-95%

Conocer M1: efecto control/efecto placebo; IC 95%

Conocer M2: la máxima pérdida de eficacia clínicamente aceptable

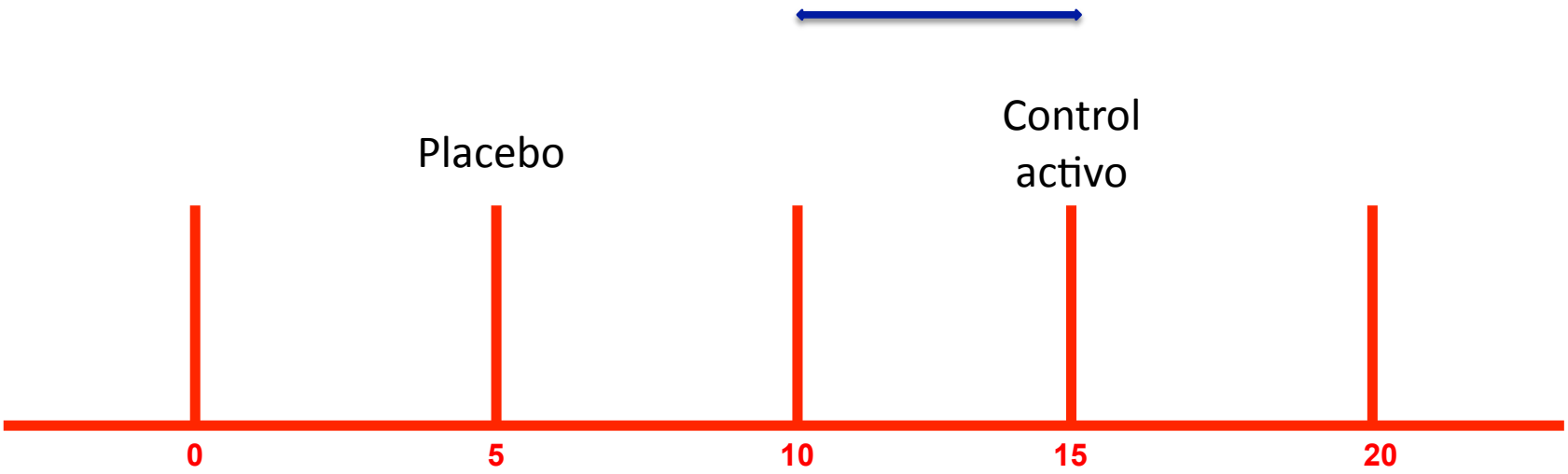
1. No puede ser mayor que el efecto del control M1.



M1 < C

Cáncer: Equivalencia 20% supervivencia
Control no lo había demostrado frente a placebo
Temple, 2008.

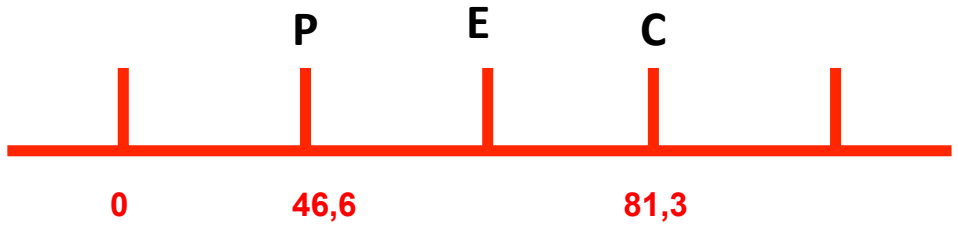
2. Debe ser inferior a la diferencia del control con placebo



$$M1 < (C-P)/2$$

M1 garantiza que se muestra un efecto superior a 0.

Fidaxomicina vs Vancomicina



81,3%-46,6%=34,7% (25,81;43,64%)
<25,81:2= 12,40%

The -10% non-inferiority margin is justified based on data from a review article by Weiss [Weiss, 2009]. The clinical success rates based on the results of tolevamer (a surrogate for placebo) and vancomycin in two well controlled Phase 3 trials showed point estimates of the risk difference of 34.7% (95% CI 25.81, 43.64) and 38.6% (95% CI 29.55, 47.73) (Table 16). Preserving 50% of the treatment difference provides a non-inferiority margin of 12.9% and 14.8%, respectively. Based on this information, a non-inferiority limit of -10% is justified.

Table 16. Non-Inferiority Margin Based on Data from Weiss, 2009

Study	Cure Rates n/N (%)		
	Tolevamer	Vancomycin	Risk Difference (%) [95% CI]
Study 301	124/266 (46.6)	109/134 (81.3)	34.7 [25.81, 43.64]
Study 302	113/268 (42.2)	101/125 (80.8)	38.6 [29.55, 47.73]

CDER

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21.04.2008
22.04.2008
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Home - 22.04.2008 - Clostridium difficile – Changing epidemiology and treatment options

Clostridium difficile – Changing epidemiology and treatment options

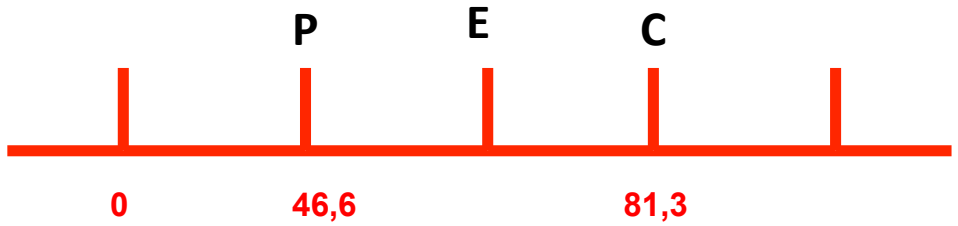
Tuesday, April 22, 2008, 10:12 - 10:24

Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with Clostridium difficile-associated diarrhoea

E. Bouza, M. Dryden, R. Mohammed, J. Peppe, S. Chasan-Taber, J. Donovan, D. Davidson, G. Short for the Polymer Alternative for CDAD Treatment (PACT) Investigators

Objectives: Clostridium difficile-associated diarrhoea (CDAD) is an increasing nosocomial problem. Treatment with vancomycin (V) or metronidazole (M) is associated with incomplete response rates, frequent recurrences, and selection for resistant bacteria. In this study, the safety and efficacy of tolevamer (T) liquid (Genzyme, Cambridge MA), a novel non-antibiotic toxin binder, was compared to V and M.
Methods: In this double-blind, multicenter (Europe, Australia, Canada) study in adult patients with acute CDAD appropriate for oral therapy, patients were randomized (2:1:1) to T 9g (3g tid, 14 days), V 500 mg (125mg qid, 10 days), or M 1500mg (375 mg qid, 10 days). In the T group, an initial 9 g loading dose was given. Patients were followed for recurrence 4 weeks after treatment cessation. The primary endpoint was non-inferiority of T vs. V for clinical success, defined as resolution of diarrhea and absence of severe abdominal discomfort due to CDAD on Day 10.
Results: 528 patients (268 T, 125 V and 135 M) comprised the intent-to-treat population. At enrollment, CDAD was noted as mild (31%), moderate (43%), or severe (25%), first occurrence (83%) or recurrent (17%), and was similar across the treatment groups. Clinical success rates were 42% (112/268) T, 81% (101/125) V, and 73 % (99/135) M, indicating similar success rates in the V and M groups (p =0.153), but a lower T success rate than V or M (p=<0.001 for both comparators). In patients with CDAD resolution sustained through the end of active treatment, the recurrence rates were 6% for T, 18% for V, and 19% for M. Adverse events were similar across treatment arms.
Conclusion: T did not meet its primary endpoint of non-inferiority vs. V. Overall, V and M had similar responses. Recurrent CDAD occurred frequently with V and M, but was uncommon among those patients who resolved with T, suggesting that flora-sparing drugs may help reduce recurrences. These results confirm those from an identically designed parallel study performed in the US and Canada (ICAAC 2007; poster 3826).

Fidaxomicina vs Vancomicina



81,3%-46,6%=34,7% (25,81;43,64%)
<25,8:2= 12,9%

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CDER

3. La inferioridad debe ser clínicamente aceptable M2

Diferencia del efecto respecto al control:

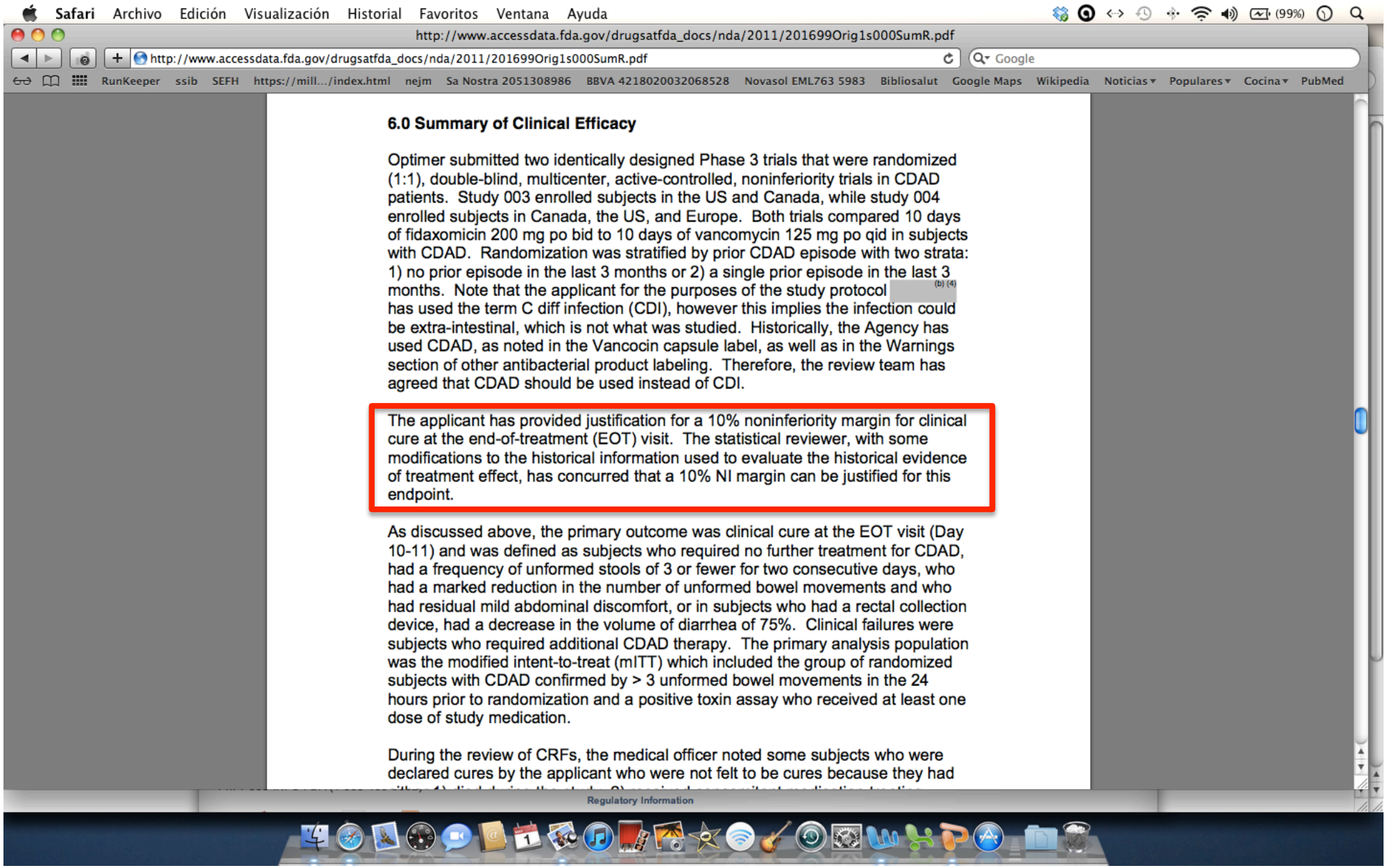
- Diferencia absoluta: infecciosas
- Fracción de la reducción riesgo: cardiovascular

7. Statistical Considerations

The choice of delta for noninferiority testing should be discussed with the Division prior to study initiation because one delta is not appropriate for all study designs. In the past, many noninferiority studies have been powered based on a delta of 10 percent to 12 percent. In most cases, this allowed sponsors to plan studies that would be reasonably powered and feasible to conduct. Such a delta has been useful when comparing the most potent component of a three-drug regimen in treatment naïve individuals. However, the sponsor should ultimately attempt to choose a delta based on prior knowledge of the quantitative contribution of the active control (substituted part of the drug regimen) to the regimen as a whole. This contribution should be determined in a similar population with a similar length of follow-up of the proposed study. For noninferiority testing, sponsors should employ two-sided 95 percent confidence intervals adjusted for multiple comparisons. If one-sided confidence intervals are used, the alpha should be 0.025.

US Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research. Guidance for industry: antiretroviral drugs using plasma HIV RNA measurements -- clinical considerations for accelerated and traditional approval. http://www.fda.gov/CDER/GUIDANCE/3647fnl.pdf (accessed May 1, 2008).

Fidaxomicina vs Vancomicina



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http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201699Orig1s000SumR.pdf

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6.0 Summary of Clinical Efficacy

Optimer submitted two identically designed Phase 3 trials that were randomized (1:1), double-blind, multicenter, active-controlled, noninferiority trials in CDAD patients. Study 003 enrolled subjects in the US and Canada, while study 004 enrolled subjects in Canada, the US, and Europe. Both trials compared 10 days of fidaxomicin 200 mg po bid to 10 days of vancomycin 125 mg po qid in subjects with CDAD. Randomization was stratified by prior CDAD episode with two strata: 1) no prior episode in the last 3 months or 2) a single prior episode in the last 3 months. Note that the applicant for the purposes of the study protocol (b) (4) has used the term C diff infection (CDI), however this implies the infection could be extra-intestinal, which is not what was studied. Historically, the Agency has used CDAD, as noted in the Vancocin capsule label, as well as in the Warnings section of other antibacterial product labeling. Therefore, the review team has agreed that CDAD should be used instead of CDI.

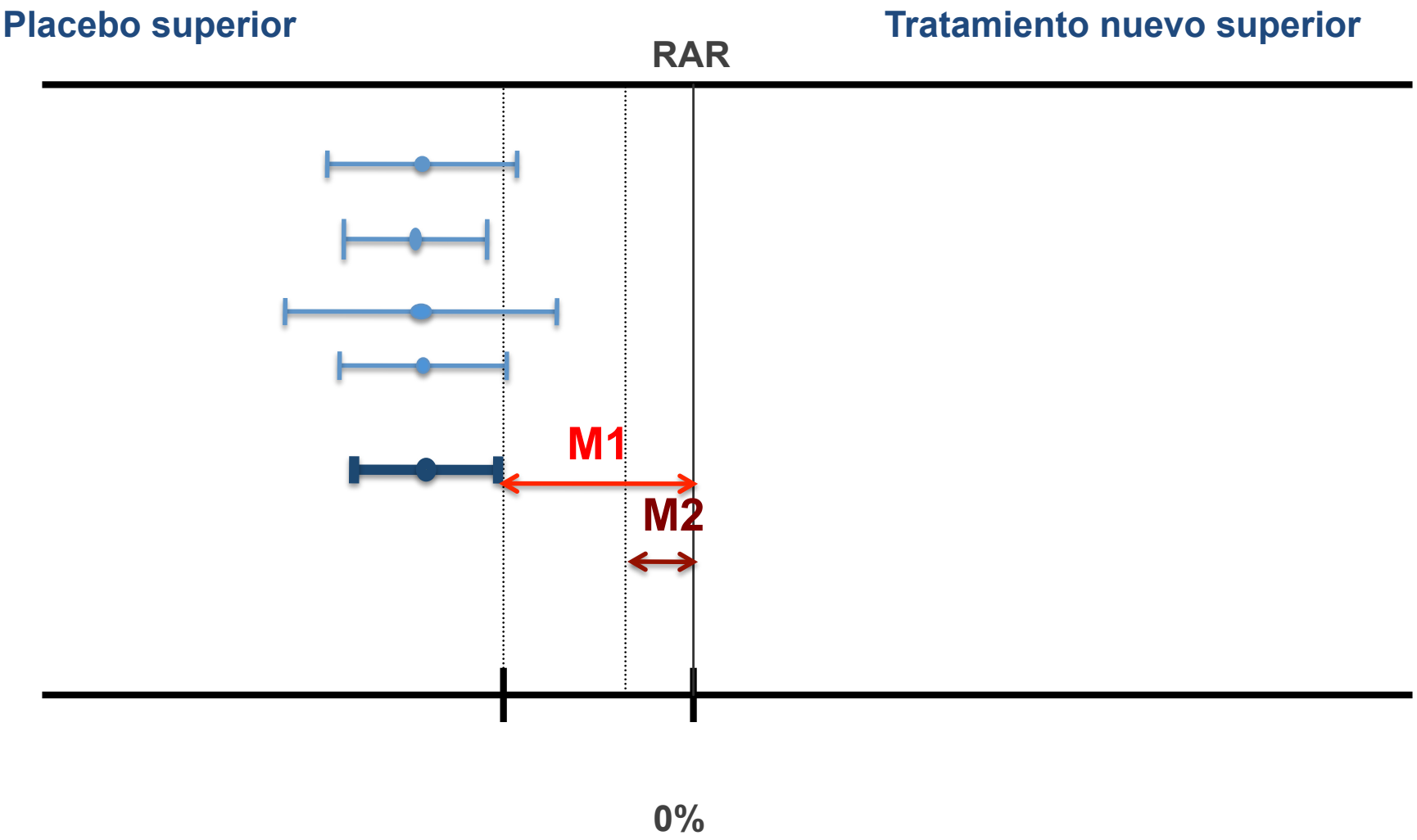
The applicant has provided justification for a 10% noninferiority margin for clinical cure at the end-of-treatment (EOT) visit. The statistical reviewer, with some modifications to the historical information used to evaluate the historical evidence of treatment effect, has concurred that a 10% NI margin can be justified for this endpoint.

As discussed above, the primary outcome was clinical cure at the EOT visit (Day 10-11) and was defined as subjects who required no further treatment for CDAD, had a frequency of unformed stools of 3 or fewer for two consecutive days, who had a marked reduction in the number of unformed bowel movements and who had residual mild abdominal discomfort, or in subjects who had a rectal collection device, had a decrease in the volume of diarrhea of 75%. Clinical failures were subjects who required additional CDAD therapy. The primary analysis population was the modified intent-to-treat (mITT) which included the group of randomized subjects with CDAD confirmed by > 3 unformed bowel movements in the 24 hours prior to randomization and a positive toxin assay who received at least one dose of study medication.

During the review of CRFs, the medical officer noted some subjects who were declared cures by the applicant who were not felt to be cures because they had

Regulatory Information

Comparación gráfica de tipos de estudios



Valores utilizados

FDA 1992 Comité Asesor Cardio Renal: recomendó la mitad del efecto del tratamiento estándar como margen de no inferioridad para nuevos **trombolíticos**

FDA Oct 2002: Guidance for Industry **Antirretrovirales**:

10-12% (RAR) del % pacientes con carga viral indetectable

FDA: **Antiinfecciosos**, delta modulable según la tasa de respuesta

Referencia	Fármacos	Indicación	Margen
Babinchak T. CID 2005;41(suppl 5):S354-67.	TIG 50mg/12h IMI 500mg/6h	Infección intraabdominal	15%
CID 2005; 41: S341-353.	TIG 50mg/12h VAN 1g+AZTREONAM 2g/12h	PPBc	15%
Arbeit. CID 2004;38:1673-81.	Daptomicina 4mg/Kg/d VAN,OXA;CLOX;NAFCI;FLUCLOX (+AZT;+METRO)	PPBc	10%
Jauregui LE. CID 2005;41:1407-15	Dalbavancin vs Linezolid	PPBc	12,5%
Fowler. N Engl J Med 2006;355;7: 653-665.	Daptomicina 6mg/Kg/d Penicilina anti-Sth o VANCO	Bacteriemia *St.aureus* Endocarditis *St.aureus*	20%

2.3 Clinical efficacy

- Ceftaroline has been shown to be as effective as (non-inferior to) standard comparator treatments in clinical trials.

cSSSI 10%

CSSTI MITT population

Trial	Ceftaroline	Vancomycin/ Aztreonam	Difference (95% CI)
CANVAS 1[1]	86.6% (304/351)	85.6% (297/347)	1.0 (-4.2, 6.2)
CANVAS 2[2]	85.1% (291/342)	85.5% (289/338)	-0.4 (-5.8, 5.0)
CANVAS 1 & 2[3]	85.9% (595/693)	85.5% (586/685)	-0.3 (-3.4, 4.0)

MITT – Modified Intention to Treat

[1] *Corey RG et al. Abs & Poster L-1515a. 48th ICAAC / 46th ISDA 2008.*
[2] *Baculik T et al. Abs & Poster #P-1792. ECCMID 2009.*
[3] *Corey RG et al. Clinical Infectious Diseases 2010; 51 (6): 641-650*

CABP 10%

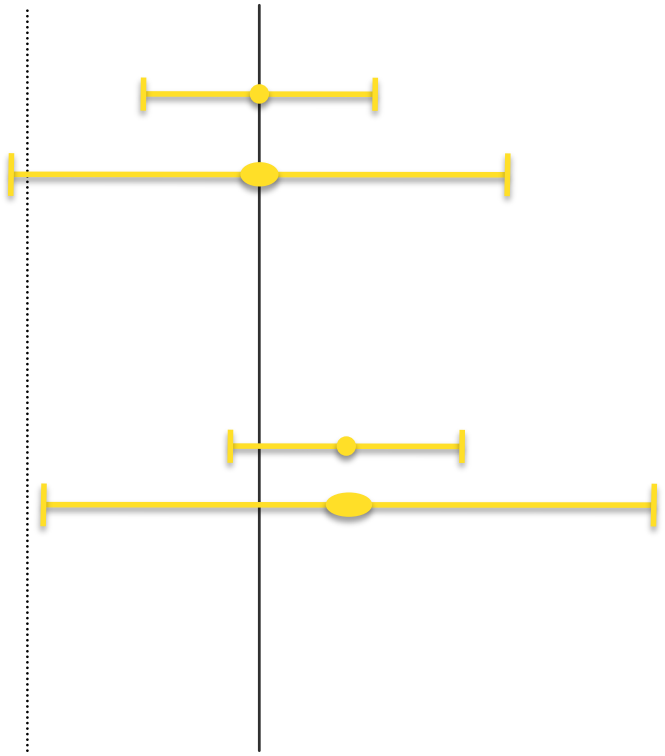
CAP MITTE population

Trial	Ceftaroline	Ceftriaxone 1g	Difference (95% CI)
FOCUS 1	83.8% (244/291)	77.7% (233/300)	6.2 (-0.2, 12.6)
FOCUS 2	81.3% (235/289)	75.5% (206/273)	5.9 (-1.0, 12.7)
FOCUS 1 & 2	82.6% (479/580)	76.6% (439/573)	6.0 (1.4, 10.7)

MITT – Modified Intention to Treat Evaluable

File TM et al. Clinical Infectious Diseases 2010; 51 (12): 1395-1405

Intervalo confianza



El valor medio de una medida no es el real

Todos los valores que engloba el IC95% de la diferencia deben estar POR ENTERO, dentro del límite de no-inferioridad.

Table 2. Clinical cure rates at test of cure.

Patient subgroup	Proportion of patients (%)		95% CI
	Moxifloxacin arm	Comparator arm	
Intent-to-treat population	293/368 (79.6)	306/365 (83.8)	−9.7 to 1.4
Per-protocol population, by PSI			
All	253/291 (86.9)	250/278 (89.9)	−8.1 to 2.2
PSI III	110/122 (90.2)	105/111 (94.6)	−11.6 to 1.9
PSI IV	120/138 (87.0)	120/134 (89.6)	−9.3 to 5.6
PSI V	23/31 (74.2)	25/33 (75.8)	−23.2 to 21.1
PSI IV/V	143/169 (84.6)	145/167 (86.8)	−9.0 to 5.8
Patients with microbiologically documented CAP			
All	114/127 (89.8)	110/123 (89.4)	−6.2 to 8.3
Pneumonia due to atypical organisms[a]	39/41 (95.1)	41/45 (91.1)	−8.3 to 14.1
Pneumococcal pneumonia[b]	69/77 (89.6)	74/85 (87.1)	−9.1 to 10.1
Patients with microbiologically valid CAP			
All	45/54 (83.3)	46/54 (85.2)	−15.4 to 11.8
Streptococcus pneumoniae–positive culture[c]	27/32 (84.4)	38/45 (84.4)	−20.0 to 12.0
Bacteremia (due to any organism)	15/20 (75.0)	18/24 (75.0)	−40.3 to 24.8

Torres A. Efficacy of Moxifloxacin in CAP. CID 2008;46(15 May):1499.

Análisis de los resultados

Superioridad: **Análisis intención tratar o según aleatorización**:

- Las pérdidas no se deben al azar
- Garantizar la comparación de los grupos
- Dificulta las diferencias

No-inferioridad: **Análisis por protocolo o de casos válidos**:

- Aumentan las diferencias
- Dificulta la conclusión de que son iguales

Ambos y detectar causas de las diferencias si las hay

Problemas de los ensayos No-inferioridad

1. Falta de HESDE (Historical evidence of sensitivity to drug effects) (ICH E-10)

HESDE cannot be determined for many symptomatic treatments, where well-designed and conducted studies often fail to distinguish drug from placebo (e.g., treatments for depression, anxiety, insomnia, angina, symptomatic heart failure, symptoms of irritable bowel disease, and pain). In those cases, there is no reason to assume that an active control would have shown superiority to a placebo (had there been one) in any given NI study, and NI studies of drugs for these treatments are not informative. This is also true for some outcome effectiveness findings, such as secondary prevention of cardiovascular disease with aspirin and post-infarction beta blockade. In the case of aspirin, the largest placebo-controlled trial (AMIS, the Aspirin Myocardial Infarction Study; see Example 3) showed no effect of aspirin at all, even though other trials all favored aspirin. Similarly, of more than 30 post-infarction beta-blocker trials, only a small number showed significantly improved survival or other cardiovascular benefit.

Problemas de los ensayos No-inferioridad

2. Asunción de la constancia del efecto

Bioscreep

Bioscreep en antiinfecciosos

Technoscreep

Riesgos de asumir la eficacia histórica

Población, criterios inclusión, tratamientos previos

- Mortalidad post-IAM por betabloqueantes está modificada por nuevos tratamientos (hipolipemiante, antiplaquetarios) o procedimientos (angioplastia)
- Efectos IECAs en ICC está modificado por uso rutinario de betabloqueantes o antagonistas aldosterona.
- Trombolítico por el momento en el que se hace

Temple RJ. FDA Experience and Perspective on Non-Inferiority Trials. FDA Workshop on CAP. January 18, 2008.

En ausencia de placebo, no se sabe si el nuevo fármaco tiene eficacia en absoluto.

Lasagna, L. Eur J Clin Pharm 1979;15:373-374.

Resultados de eficacia clara:

- Heparina TVP
- UTI
- Leucemia aguda, Ca testicular
- Betaagonistas broncoespasmo
- Profilaxis asma con corticoides
- Trombolíticos IAM

Para la mayoría de los tratamientos sintomáticos, no se ha visto efecto en EECCs:

Ansiedad	Síntomas ICC
Depresión	Angina
Insomnio	GERD reflujo gastroesofágico
Rinitis alérgica	Síndrome intestino irritable
Profilaxis asma	Dolor

Temple RJ. FDA Experience and Perspective on Non-Inferiority Trials. FDA Workshop on CAP. January 18, 2008.

Problemas de los ensayos No-inferioridad

3. Falta de sensibilidad

ARCHIVES OF
OTOLARYNGOLOGY–
HEAD & NECK SURGERY

Volume 124(8) August 1998 pp 879-885

Homeopathic vs Conventional Treatment of Vertigo:
A Randomized Double-blind Controlled Clinical Study

Weiser, Michael MBChB; Strosser, Wolfgang MD, MBChB; Klein, Peter MSc

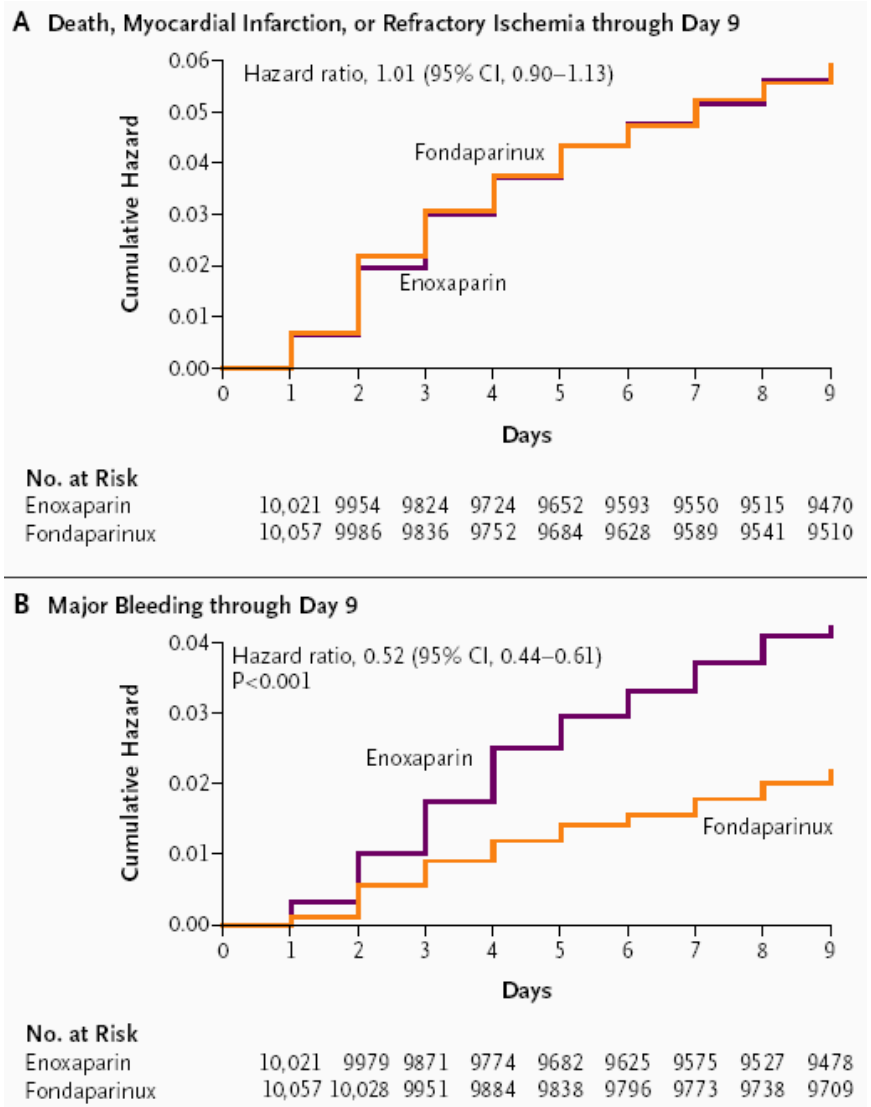
Nuevas aproximaciones

Diseños adaptativos

- Objetivo
- Tamaño muestral
- M2 flexibles

Diseños combinados

Ensayos, objetivos, variables mixtas



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators*

Eficacia:
5,8 frente 5,7

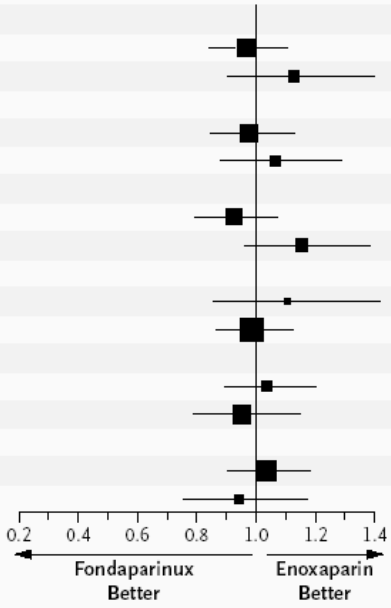
Hazard Ratio 1,01 (0.90-1.13)

Seguridad: 2,2% frente 4,1%
Hazard Ratio 0,52 (0,44 a 0,61)

A Primary Efficacy at 9 Days

Characteristic	No. of Patients	Percentage of Patients with Event		Interaction P Value
		Enoxaparin	Fondaparinux	
Age				
≥65 yr	12,261	6.8	6.6	
<65 yr	7,814	4.0	4.4	0.25
Sex				
Male	12,379	6.0	5.8	
Female	7,699	5.3	5.7	0.48
Creatinine				
At or above median	11,124	6.4	5.9	
Less than median	8,871	4.9	5.6	0.07
Heparin at randomization				
Yes	3,566	6.5	7.1	
No	16,512	5.6	5.5	0.43
Revascularization in 9 days				
Yes	7,372	9.6	9.9	
No	12,706	3.5	3.3	0.47
Catheterization laboratory in center				
Yes	14,028	5.9	6.0	
No	6,050	5.4	5.1	0.48

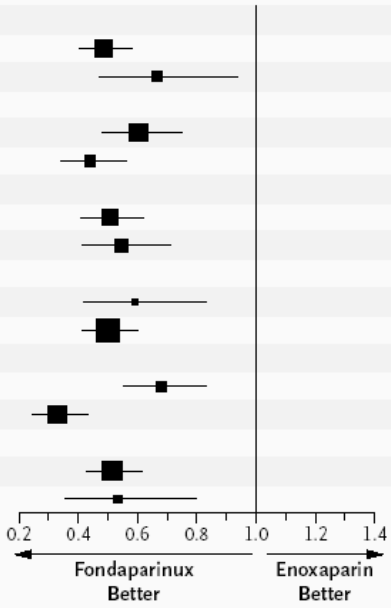
Hazard Ratio



B Major Bleeding at 9 Days

Characteristic	No. of Patients	Percentage of Patients with Event		Interaction P Value
		Enoxaparin	Fondaparinux	
Age				
≥65 yr	12,261	5.5	2.7	
<65 yr	7,814	2.1	1.4	0.11
Sex				
Male	12,379	3.3	2.0	
Female	7,699	5.5	2.5	0.07
Creatinine				
At or above median	11,124	4.7	2.4	
Less than median	8,871	3.4	1.9	0.71
Heparin at randomization				
Yes	3,566	5.0	3.0	
No	16,512	4.0	2.0	0.35
Revascularization in 9 days				
Yes	7,372	6.0	4.2	
No	12,706	3.0	1.0	<0.001
Catheterization laboratory in center				
Yes	14,028	5.0	2.6	
No	6,050	2.3	1.2	0.88

Hazard Ratio



Los estudio de NI se han constituido como ensayos de referencia:
-Pueden mostrar superioridad
-Tienen connotación clínica

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 27 July 2000
CPMP/EWP/482/99

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON SWITCHING BETWEEN SUPERIORITY AND NON-INFERIORITY

STATISTICAL ANALYSIS

The primary efficacy analysis was based on the intention-to-treat approach, with the use of data from all patients who underwent randomization. First, the noninferiority of posaconazole as compared with fluconazole or itraconazole therapy was assessed. For our study, the incidence of proven or probable invasive fungal infection was assumed to be 8% or less with fluconazole or itraconazole prophylaxis.[1] Therefore, using a cutoff level of significance of 4.87% for the final analysis (in order to account for the interim analysis), we calculated that if the upper bound of the 95.13% confidence interval (hereafter called the 95% CI) for the difference between the incidence of proven or probable fungal infection for posaconazole and that for fluconazole or itraconazole was less than 4%, noninferiority would be demonstrated, and the superiority of posaconazole over fluconazole or itraconazole therapy could be assessed. The superiority of posaconazole would be established if the upper bound of the same 95% CI was negative. This two-step analysis allowed for an overall type 1 error rate of 0.05. We used the Kaplan–Meier method to evaluate time to death from any cause, time to death related to fungal infection, time to proven or probable fungal infection, time to first use of empirical antifungal therapy, and survival free from proven or probable invasive fungal infection. The survival benefit was assessed with the chi-square and log-rank tests. All analyses except the noninferiority analysis were based on two-sided P values, with a two-sided P value of less than 0.05 considered to indicate statistical significance. The numbers of patients who would need to be treated to prevent one fungal infection and one death (numbers needed to treat) were calculated as described pre-

Proven or probable invasive fungal infections occurred during the treatment phase in 7 of the 304 patients (2%) in the posaconazole group and in 25 of the 298 patients (8%) in the fluconazole or itraconazole group (absolute reduction in the posaconazole group, −6%; 95% CI, −9.7 to −2.5; P<0.001). The superiority of posaconazole over fluconazole was confirmed in a post hoc analysis limited to centers at which fluconazole was used as the comparison study drug (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). We estimated that 16 patients would need to be treated with posaconazole, as compared with fluconazole or itraconazole, in order to prevent one invasive fungal infection.

During the 100-day period after randomization, 14 of 304 patients (5%) in the posaconazole group had a proven or probable fungal infection, as compared with 33 of 298 patients (11%) in the fluconazole or itraconazole group (P=0.003). The mean (±SD) time to invasive fungal infection was 41±26 days in the posaconazole group and 25±26 days in the fluconazole or itraconazole group. Kaplan–Meier analysis of the time to invasive fungal infection showed a significant difference in favor of posaconazole (P=0.003) (Fig. 1A). Table 2 lists the causative pathogens of invasive fungal infections that occurred during the treatment phase; aspergillus was the most common. There were significantly fewer cases of aspergillosis associated with posaconazole prophylaxis than with fluconazole or itraconazole prophylaxis (2 [1%] vs. 20 [7%], P<0.001).

CLINICAL SUCCESS OR FAILURE

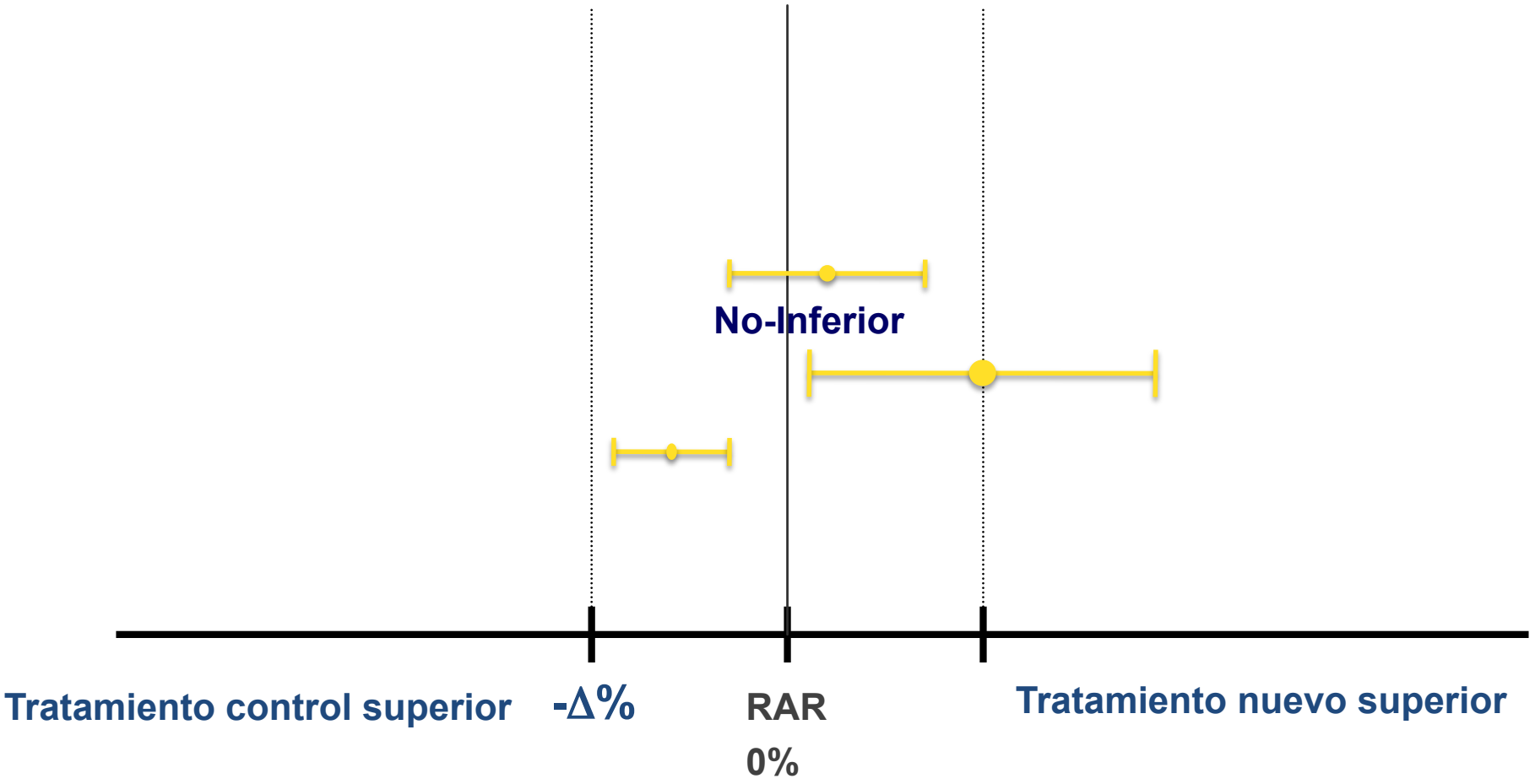
Rates of clinical success or failure and the reasons for clinical failure are listed in Table 3. Of the 304 patients in the posaconazole group, 81 (27%)

Cornely OA. Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia. N Engl J Med 2007;356:348-59.

Cambio de objetivo

No-inferioridad ⇄ Superioridad

Análisis de los datos AIT y PP



Calidad

SPECIAL COMMUNICATION

Reporting of Noninferiority and Equivalence Randomized Trials

An Extension of the CONSORT Statement

Gilda Piaggio, PhD
Diana R. Elbourne, PhD
Douglas G. Altman, DSc
Stuart J. Pocock, PhD
Stephen J. W. Evans, MSc
for the CONSORT Group

The CONSORT (Consolidated Standards of Report
cluding a checklist and a flow diagram, was devel
prove their reporting of randomized controlled tri
on individually randomized trials with 2 parallel gr
sible superiority of one treatment compared with
extended to other trial designs. Noninferiority an
methodological features that differ from superior
ticular difficulties in design, conduct, analysis, and
the rationale for such trials occurs frequently, thos
specifically as noninferiority or equivalence trials
the medical literature. The quality of reporting of t
often inadequate. In this article, we present an ad
list for reporting noninferiority and equivalence t
tive examples and explanations for those items ar
CONSORT checklist. The intent is to improve repo
equivalence trials, enabling readers to assess the v
conclusions.

JAMA. 2006;295:1152-1160

THE CONSOLIDATED STANDARDS of Reporting Trials (CONSORT) statement was developed to alleviate the problem of inadequate reporting of randomized controlled trials (RCTs),[1-4] which has been associated with biased treatment effects.[5-7] The statement comprises evidence-based recommendations for reporting RCTs, including a flowchart of participants through the trial.

CONSORT's primary focus is on parallel group trials,[1-3] aiming to identify treatment superiority if it really exists. Most CONSORT recommendations apply equally well to other trial designs, but some need adaptation. Herein we extend the CONSORT recommendations to noninferiority and equivalence trials. First, we explain the rationale for and key methodological features of such trials. Second, we consider how commonly noninferiority and equivalence trials are published and provide empirical evidence about their quality. Last, we present an adapted CONSORT checklist for reporting noninferiority and equivalence trials and give illustrative examples (and further elaboration) for those items that have been amended.

See also pp 1147 and 1172.

For convenience, we will refer to *treatments* and *patients*, although we recognize that not all interventions evaluated in RCTs are technically treatments and the participants in trials are not always patients.

Rationale for Noninferiority or Equivalence Designs

Most RCTs aim to determine whether one intervention is superior to another. By contrast, equivalence trials[8] aim to determine whether one (typically new)
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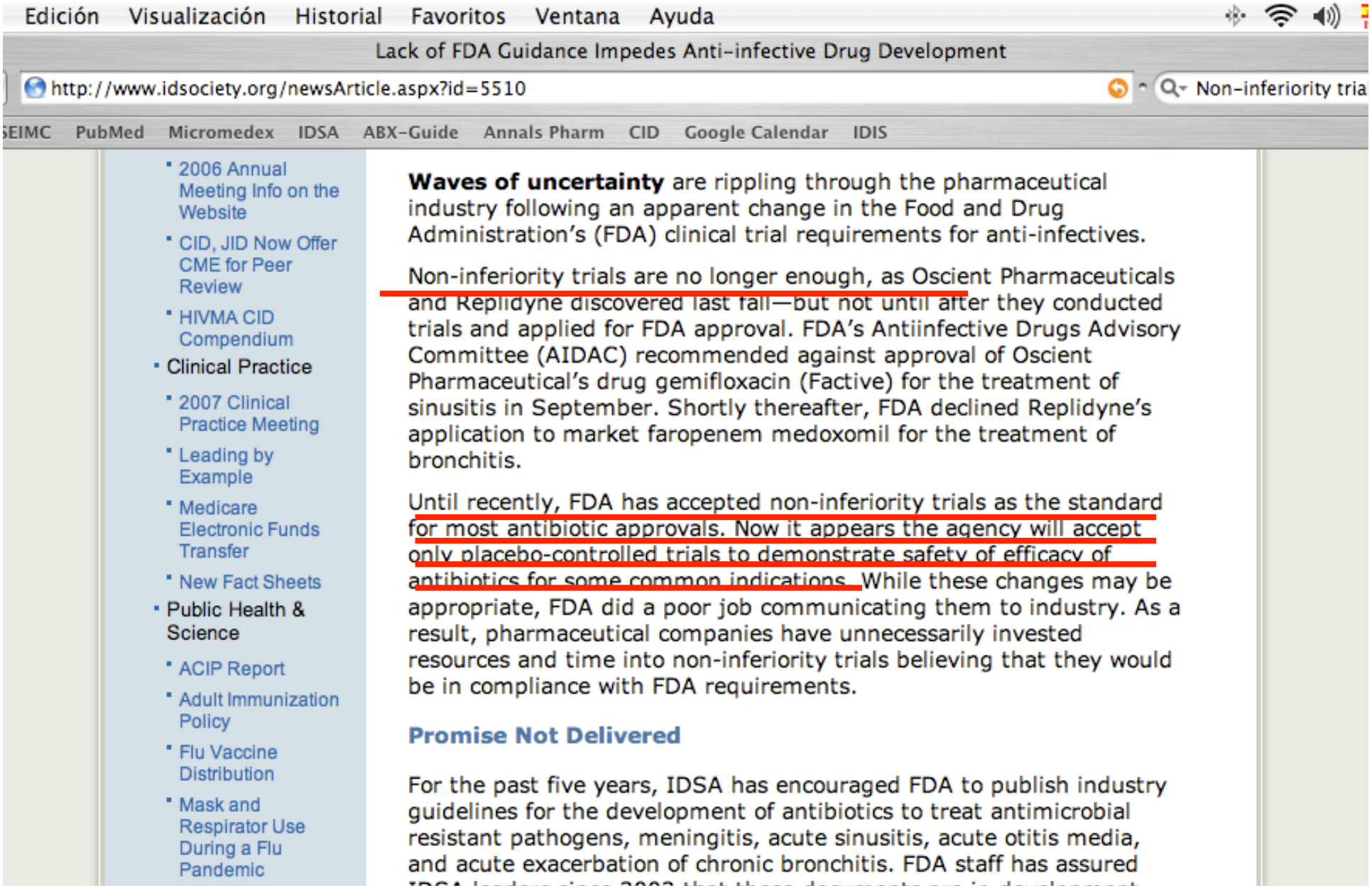
Table. Checklist of Items for Reporting Noninferiority or Equivalence Trials (Additions or Modifications to the CONSORT Checklist are Shown in Italics)

Paper Section and Topic	Item Number	Descriptor (Adapted for Noninferiority or Equivalence Trials)
Title and abstract	1*	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned"), *specifying that the trial is a noninferiority or equivalence trial.*
Introduction		
Background	2*	Scientific background and explanation of rationale, *including the rationale for using a noninferiority or equivalence design.*
Methods		
Participants	3*	Eligibility criteria for participants *(detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment)* and the settings and locations where the data were collected.
Interventions	4*	Precise details of the interventions intended for each group, *detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered.
Objectives	5*	Specific objectives and hypotheses, *including the hypothesis concerning noninferiority or equivalence.*
Outcomes	6*	Clearly defined primary and secondary outcome measures, *detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).
Sample size	7*	How sample size was determined, *detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules *(and whether related to a noninferiority or equivalence hypothesis).*
Randomization		
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12*	Statistical methods used to compare groups for primary outcome(s), *specifying whether a 1- or 2-sided confidence interval approach was used.* Methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results		
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analyzed	16*	Number of participants (denominator) in each group included in each analysis and whether *"intention-to-treat" and/or alternative analyses were conducted.* State the results in absolute numbers when feasible (eg, 10/20, not 50%).
Outcomes and estimation	17*	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval). *For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
Comment		
Interpretation	20*	Interpretation of the results, taking into account the *noninferiority or equivalence hypothesis and any other* trial hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.
Generalizability	21	Generalizability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

*Expansion of corresponding item on CONSORT checklist.[2,3]



Gemifloxacino: sinusitis (nov 2007)

Faropenem: bronquitis

Gato Cheshire, “*todos estamos locos*”**.**

- Has de estarlo a la fuerza, de lo contrario no habrías venido aquí.

Muchas gracias