Sacro Cuore Don Calabria
Cancer Care Center
Negrar - Verona

Con il Patrocinio di

AIOM Associazione Italiana di Oncologia Medica
SIMIT Società Italiana di Malattie Infettive e Tropicali
SIMET
RAO

STUDI CLINICI: METODOLOGIA

Coordinatore:
Dr.ssa Stefania Gori

Evento ECM MODULO 1
(formazione di base)
"A good foundation"

NEGRAR
7-8 Settembre 2016

Centro Formazione
Ospedale Sacro Cuore
Don Calabria

7 Settembre

ore 09,40-09,55 Introduzione al Corso FABRIZIO NICOLIS

ore 09,55-10,00 Presentazione del Corso STEFANIA GORI

ore 10,00-10,15 Il quesito clinico come *primum movens* di ogni sperimentazione

ore 10,15-10,45 Plausibilità e rilevanza dello studio

ore 10,45-11,30 What?, so what?, now what?

ore 11,30-12,30 Il disegno dello studio: studi osservazionali e studi sperimentali; scelta del braccio di controllo e procedure di randomizzazione

ore 12,30-13,15 What?, so what?, now what?

ore 13,15-14,15 *Colazione di lavoro*

ore 14,15-15,45 Variabili statistiche: misure di effetto relative e assolute

ore 15,45-16,30 What?, so what?, now what?

ore 16,30-16,45 *Pausa caffè*

ore 16,45-17,45 Scelta dell'endpoint in base al quesito e al disegno dello studio; endpoints surrogati

ore 17,45-18,30 What?, so what?, now what?

8 Settembre

ore 08,30-09,00 Principi di dimensionamento campionario (1): gli errori statistici

ore 09,00-10,15 What?, so what?, now what?

ore 10,15-10,45 Principi di dimensionamento campionario (2): il *target* di rilevanza clinica

ore 10,45-11,30 What?, so what?, now what?

ore 11,30-11,45 *Pausa caffè*

ore 11,45-12,15 Principi di dimensionamento campionario (3): calcolo del campione per i diversi tipi di variabili statistiche

ore 12,15-13,00 What?, so what?, now what?

ore 13,00-13,15 *Prova scritta ECM e chiusura del Corso*

Superiorità Vs Non-inferiorità

Si ritiene che il trattamento in esame "A" abbia le potenzialità per migliorare il trattamento standard "B" almeno di una quantità Δ

studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

A < B non oltre una quantità M di rilevanza clinica

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

Annals of Oncology 26: 1547–1573, 2015

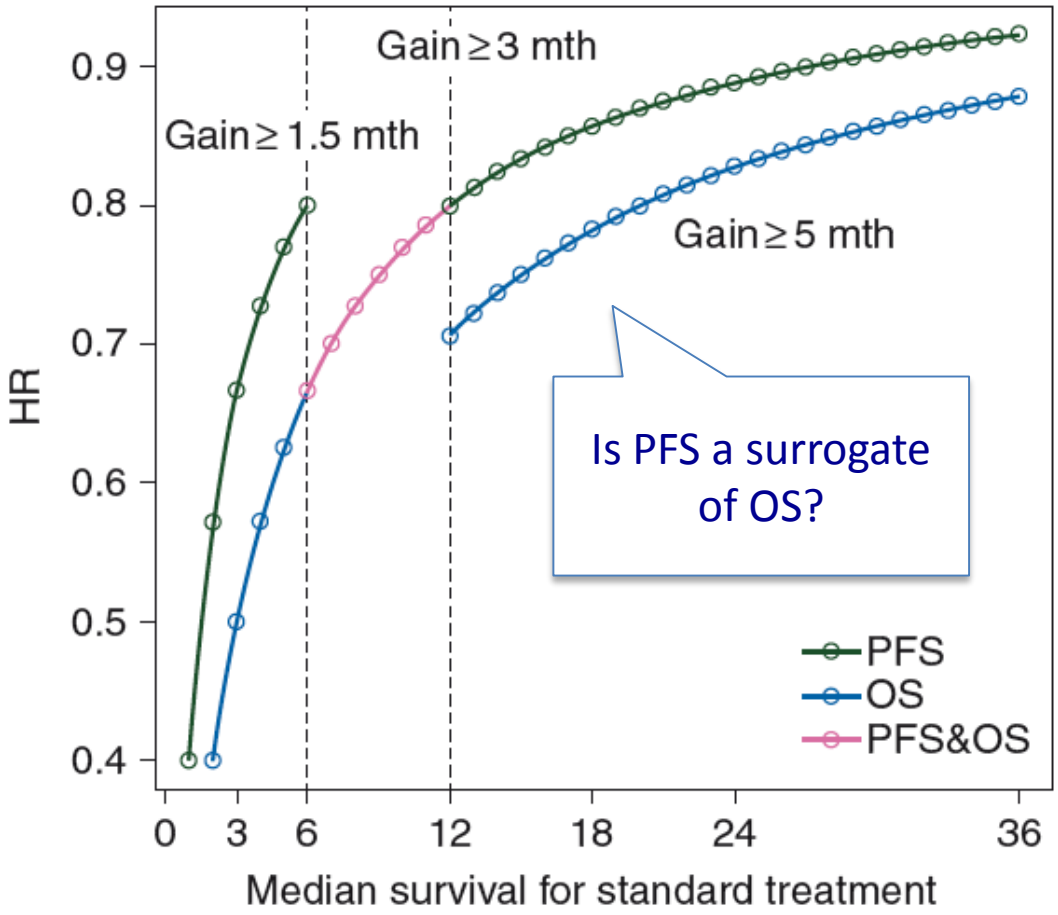
In the absence of a standardised approach for grading the magnitude of clinical benefit, conclusions and recommendations derived from studies are often hotly disputed and very modest incremental advances have often been presented, discussed and promoted as major advances or 'breakthroughs'.

The European Society for Medical Oncology (ESMO) has developed a validated and reproducible tool to assess the magnitude of clinical benefit for cancer medicines, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS). This tool uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment.

A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherny[1*], R. Sullivan[2], U. Dafni[3], J. M. Kerst[4], A. Sobrero[5], C. Zielinski[6], E. G. E. de Vries[7] & M. J. Piccart[8,9]

Annals of Oncology 26: 1547–1573, 2015



The correspondence between an HR value and the minimum absolute gain in months considered as beneficial according to the ESMO-MCBS by median survival (OS or PFS) for control

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Recommended Targets for Meaningful Clinical Trial Goals

			Primary End Point		Secondary End Point	
Cancer Type	Patient Population	Current Baseline Median OS (months)	Improvement Over Current OS That Would Be Clinically Meaningful (months)	Target HRs	Improvement in 1-Year Survival Rate (%)*	Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Is PFS a surrogate of OS?

Ellis LM et al, JCO 2014

American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options

THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

Step 1: Determine the regimen's CLINICAL BENEFIT							
1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.D.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. Proceed to 1.C.						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Schnipper LE, et al, JCO 2015

When Are "Positive" Clinical Trials in Oncology Truly Positive?

Alberto Ocana, Ian F. Tannock

J Natl Cancer Inst 2011;103:16–20

We would define a positive trial as one in which the predefined value of *delta* represents a clinically important difference in an endpoint that directly reflects benefit (mainly OS or quality of life) to patients and for which the results provide a best estimate of the difference that exceeds that predefined value of *delta*. Consistent with a recent commentary suggesting the need to increase the value of *delta* in future clinical trials, we provide an estimate of *delta* that would be generally accepted as representing a minimum clinically important difference in the primary endpoint: approximately 3 months increase in median OS for patients with advanced metastatic solid tumors (usually corresponding to an hazard ratio of approximately 0.75).

Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial

Evan A Stein, Dan Gipe, Jean Bergeron, Daniel Gaudet, Robert Weiss, Robert Dufour, Richard Wu, Robert Pordy
Lancet 2012; 380: 29–36

Sample size and power calculations were based on the ability to detect a treatment difference in LDL-C of 40% from baseline to week 12 with a standard deviation range of 20–30% from the completed phase 1 studies.[14]

Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: Results of a 24 week, double-blind, randomized Phase 3 trial

Eli M. Roth [a,*], Marja-Riitta Taskinen [b], Henry N. Ginsberg [c], John J.P. Kastelein [d], Helen M. Colhoun [e], Jennifer G. Robinson [f], Laurence Merlet [g], Robert Pordy [h], Marie T. Baccara-Dinet [i]

International Journal of Cardiology 176 (2014) 55–61

A sample size of 45 patients per treatment arm was calculated to have 95% power to detect a mean difference between alirocumab and ezetimibe of 20% in LDL-C percent change from baseline to week 24 using a 2-sided *t*-test with 5% significance, assuming a common standard deviation (SD) of 25% based on a previous alirocumab trial [1] and with an expected rate of exclusion of 5%.

Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis

Paul O'Connor, M.D., Jerry S. Wolinsky, M.D., Christian Confavreux, M.D., Giancarlo Comi, M.D., Ludwig Kappos, M.D., Tomas P. Olsson, M.D., Ph.D., Hadj Benzerdjeb, M.D., Philippe Truffinet, M.D., Lin Wang, Ph.D., Aaron Miller, M.D., and Mark S. Freedman, M.D., for the TEMSO Trial Group*

N Engl J Med 2011;365:1293-303

A sample of 360 randomly assigned patients per group was required to provide 95% statistical power to detect relative risk reductions of 25% in the annualized relapse rate after 2 years, assuming an annualized relapse rate of 0.74 for the group receiving placebo and a standard deviation of 0.626.

High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction

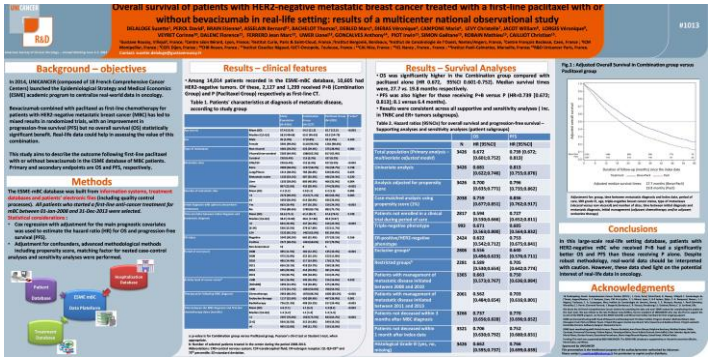
The IDEAL Study: A Randomized Controlled Trial

Terje R. Pedersen, MD, PhD
Ole Faergeman, MD, DMSc
John J. P. Kastelein, MD, PhD
Anders G. Olsson, MD, PhD
Matti J. Tikkanen, MD, PhD
Ingar Holme, PhD
Mogens Lytken Larsen, MD, DMSc
Fredrik S. Bendiksen, MD
Christina Lindahl, MD
Michael Szarek, MS
John Tsai, MD

JAMA. 2005;294:2437-2445

The primary clinical outcome was time to first occurrence of a major coronary event, defined as coronary death, hospitalization for nonfatal acute myocardial infarction, or cardiac arrest with resuscitation.

The trial was designed to have 90% power to detect an anticipated 21% relative risk reduction (from 10% to 7.9%) in the primary outcome variable with atorvastatin over 5 years using a 2-tailed α level of .05.



		OS
	N	**HR [95%CI]**
Total population (*Primary analysis – multivariate adjusted model*)	**3426**	**0.672 [0.601;0.752]**
Analysis adjusted for propensity score	**3426**	**0.700 [0.635;0.771]**
Case-matched analysis using propensity score (1%)	**2038**	**0.759 [0.677;0.851]**

Table 2. Maximal preliminary scores

Treatments with non-curative intent (form 2)

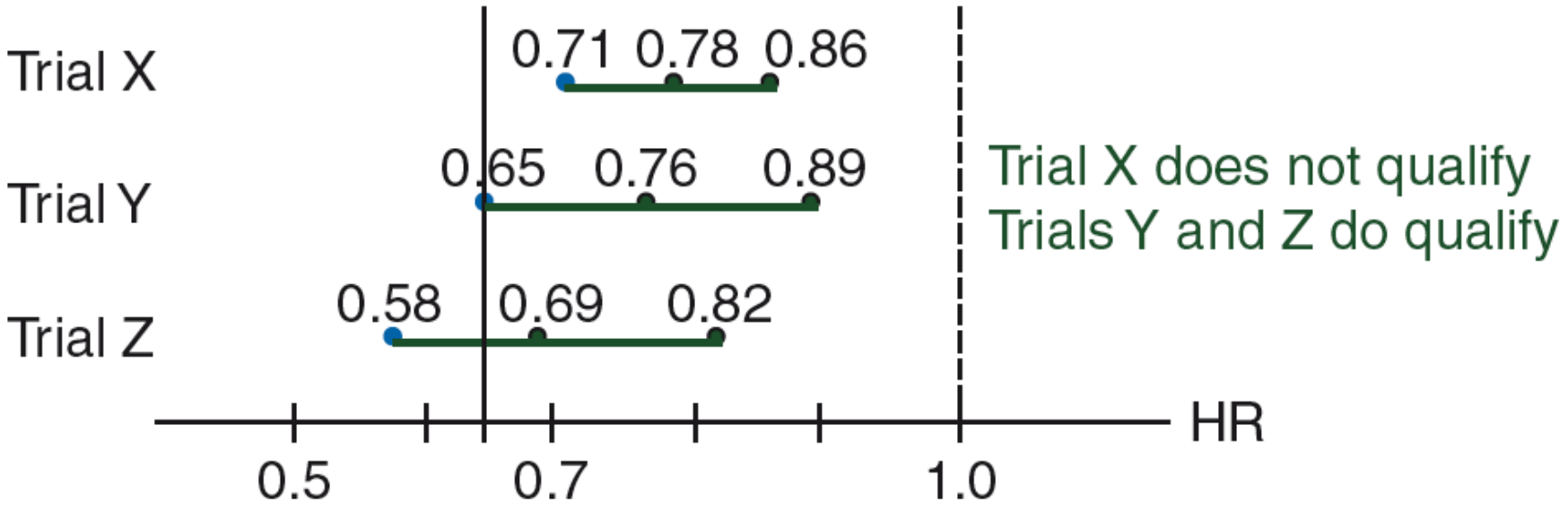
Primary outcome OS (form 2a)

Control ≤12 months

HR ≤0.65 *AND* gain ≥3 months *OR*

Control >12 months

HR ≤0.70 *AND* gain ≥5 months *OR*



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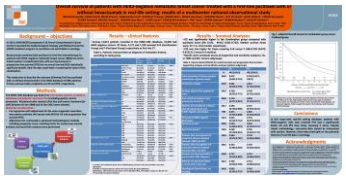
Annals of Oncology 26: 1547–1573, 2015

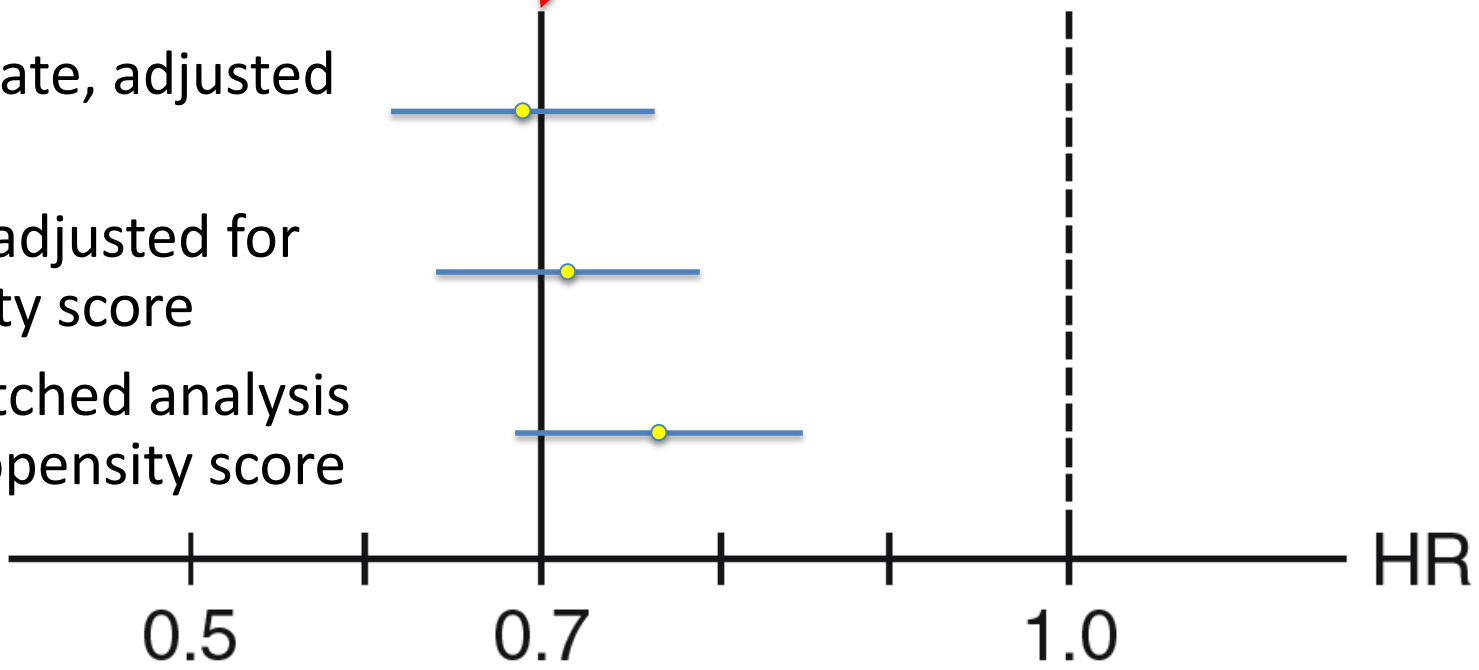


Soglia di rilevanza clinica raggiunta per tutte le tipologie di analisi

Multivariate, adjusted model

Analysis adjusted for propensity score

Case-matched analysis using propensity score



The Minimal Clinical Interesting Difference (M.C.I.D.)

- **it's easily understood by clinicians as a key concept in the interpretability of PRO scores;**
- **will inform judgments about the success-fulness of an intervention;**
- **an individual patient achieving the score equal or greater than the MCID might be considered a beneficiary of the intervention, what would lead to the definition of a responder.**

Estimating a minimal clinically important difference for the EuroQol 5-dimension health status index in persons with multiple sclerosis

Christine G Kohn[1,2], Matthew F Sidovar[3], Kirandeep Kaur[1], Yungfen Zhu[1] and Craig I Coleman[1,2*]

Health and Quality of Life Outcomes 2014, **12**:66

In conclusion, the MCID estimate calculated in this study can aid researchers and clinicians when discriminating between patient groups for EQ-5D index scores of PwMS. Our MCID range of 0.050-0.084 for EQ-5D was within the range of MCID estimates of other disease states. In general, patients who have severe disability had higher MCIDs than patients who had mild-moderate disability.

eriorità

Vista la migliore tollerabilità del trattamento in esame “A”, si è disposti ad accettarne una eventuale minore efficacia rispetto al trattamento standard “B” purché questa non vada oltre un margine M

studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

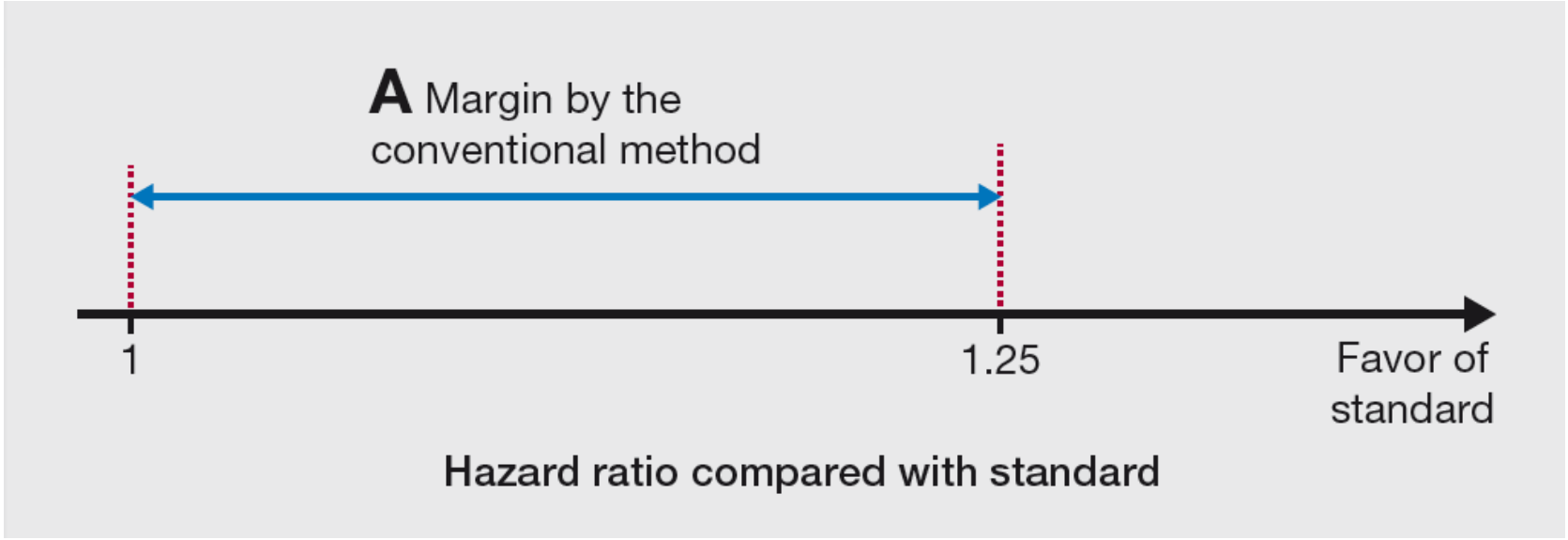
A < B non oltre una quantità M di rilevanza clinica

Statistical Issues and Recommendations for Noninferiority Trials in Oncology: A Systematic Review

Shiro Tanaka[1], Yousuke Kinjo[2], Yoshiki Kataoka[2], Kenichi Yoshimura[1], and Satoshi Teramukai[1]

Clin Cancer Res; 18(7); 1837–47. ©2012 AACR.

Fixed Margin Method



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

London, 27 July 2005

Doc. Ref. EMEA/CPMP/EWP/2158/99

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN

In order to demonstrate non-inferiority, the recommended approach is to pre-specify a margin of non-inferiority in the protocol.

After study completion, a two-sided 95% confidence interval (or one-sided 97.5% interval) for the true difference between the two agents will be constructed. This interval should lie entirely on the positive side of the non-inferiority margin.

The choice of delta must always be justified on both clinical and statistical grounds. It always needs to be tailored specifically to the particular clinical context and no rule can be provided that covers all clinical situations.

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Rene Belder, M.D., Steven V. Joyal, M.D., Karen A. Hill, B.A., Marc A. Pfeffer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators*

N Engl J Med 2004;350:1495-504.

The study was designed to establish the noninferiority of pravastatin as compared with atorvastatin with respect to the time to an end-point event.

For the comparison of pravastatin with atorvastatin, we defined the prespecified boundary for noninferiority as an upper limit of the one-sided 95 percent confidence interval of the relative risk at two years of less than 1.17 (corresponding to a hazard ratio throughout follow-up of 1.198).

Highlights from the Tenth World Conference on Lung Cancer

TRACEY L. EVANS

The University of Pennsylvania Medical Center—Presbyterian, Division of Hematology/Oncology, Philadelphia, Pennsylvania, USA

The Oncologist 2004;9:232-238

	Pemetrexed (n = 283)	Docetaxel (n = 288)
Median survival	8.3 months	7.9 months
Hazard ratio* (95% CI)	0.99 (0.8-1.2)	
1-year survival rate	29.7%	29.7%

*This study was initially designed to be a noninferiority trial using the fixed margin method. Using this statistical test, pemetrexed would be declared no worse than 10% less efficacious than docetaxel if the upper limit of the 95% CI of the overall survival hazard ratio was ≤1.11. The upper limit of the hazard ratio observed in the study was 1.2. By another retrospectively applied test of noninferiority, the percent retention method, the comparator must demonstrate preservation of no less than 50% of the benefit of the standard arm. Pemetrexed in this study had a 102% retention of efficacy (95% CI = 52%-157%, p value = 0.047). Therefore, by this test, pemetrexed would be declared noninferior.

Statistical Review Addendum #1

Medical Division: Oncology Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)
NDA NUMBER: NDA 21-677 / N000
DRUG NAME: Alimta (Pemetrexed, LY231514)
INDICATION: Locally advanced or metastatic non-small cell lung cancer
SPONSOR: Eli Lilly and Company

3. Based on our internal discussion, we have determined that the lower limit of the 95% confidence interval is probably too conservative for estimating the control treatment (docetaxel) effect; thus, the resulting statistical test used in the statistical review dated 6/29/04 is also probably too conservative.

Design and analysis of non-inferiority mortality trials in oncology

Mark Rothmann[1,*,†], Ning Li[1], Gang Chen[1], George Y. H. Chi[1], Robert Temple[2] and Hsiao-Hui Tsou[1]

Statist. Med. 2003; **22**:239–264 (DOI: 10.1002/sim.1400)

Good Enough: A Primer on the Analysis and Interpretation of Noninferiority Trials

Sanjay Kaul, MD, and George A. Diamond, MD

Ann Intern Med. 2006;145:62-69

Active-control noninferiority trials are being performed with increasing frequency, especially in cardiovascular and oncologic applications when placebo-controlled trials are considered unethical.

Because of this uncertainty, the noninferiority margin is typically defined in terms of some fraction (f) of the standard treatment effect to be preserved (9, 11).

In the context of oncologic and thrombolytic trials, when mortality is evaluated, the U.S. Food and Drug Administration has suggested an f value of 0.5 (9, 11, 16).

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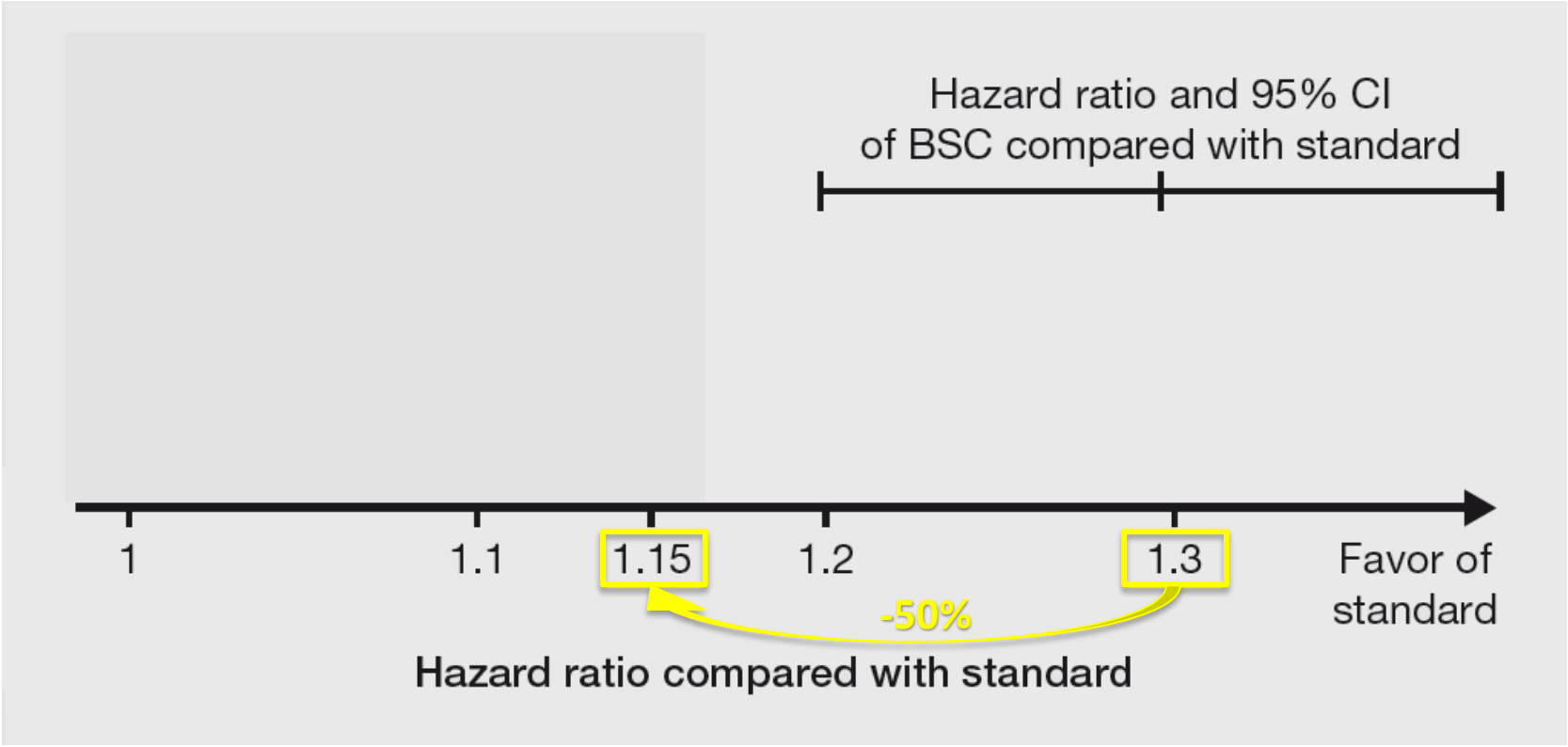
Percent Retention Method



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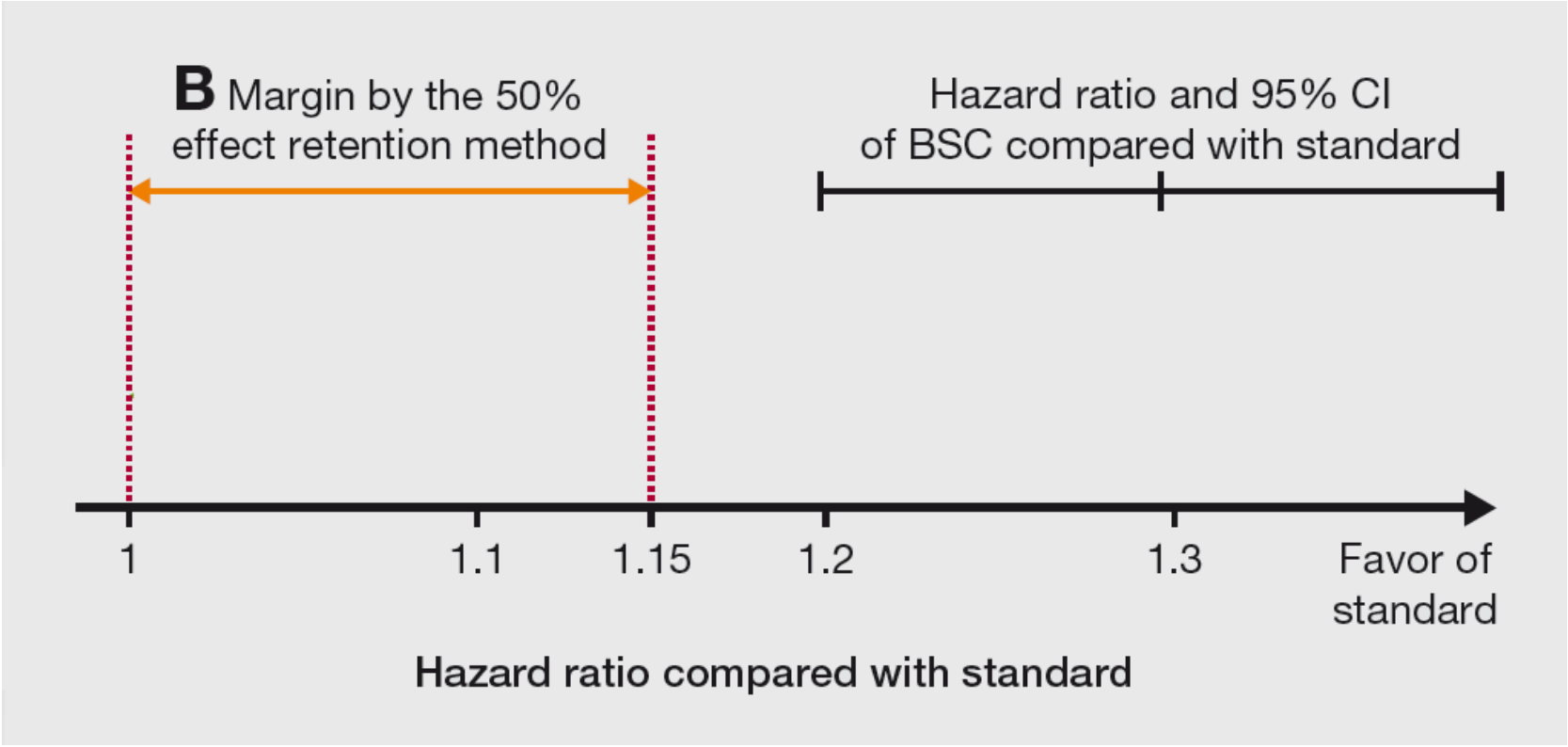

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Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy

Nasser Hanna, Frances A. Shepherd, Frank V. Fossella, Jose R. Pereira, Filippo De Marinis, Joachim von Pawel, Ulrich Gatzemeier, Thomas Chang Yao Tsao, Miklos Pless, Thomas Muller, Hong-Liang Lim, Christopher Desch, Klara Szondy, Radj Gervais, Shaharyar, Christian Manegold, Sofia Paul, Paolo Paoletti, Lawrence Einhorn, and Paul A. Bunn Jr.

J Clin Oncol 22:1589-1597. © 2004 by American Society of Clinical Oncology

the hypothesis that pemetrexed retained ≥ 50% of the survival benefit of docetaxel over BSC using data from the randomized comparative trial of docetaxel versus BSC by Shepherd et al[5] was prospectively planned (percent retention method).[14]

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

10.1056/NEJMoa1107039 NEJM.ORG

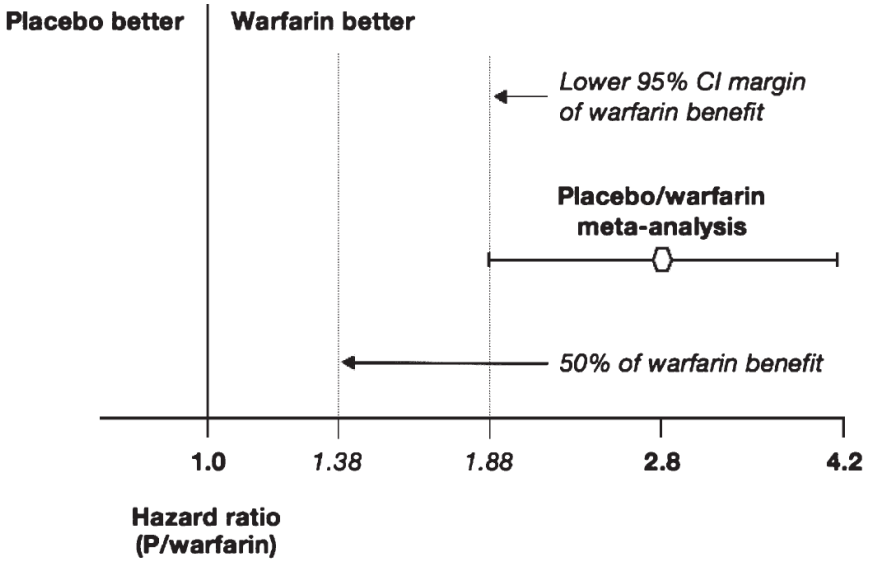
The primary noninferiority hypothesis required that apixaban preserve at least 50% of the relative reduction in the risk of stroke or systemic embolism associated with warfarin (62%) in six previous, major randomized, controlled trials.[10] This hypothesis provided a lower 95% confidence interval of 1.88 for the relative risk with placebo as compared with warfarin, and one half of this value was 1.44 (or 1.38 on a log scale).

Antithrombotic drug development for atrial fibrillation: Proceedings, Washington, DC, July 25-27, 2005

Kevin Jackson, MD,[a] Bernard J. Gersh, MB, ChB, DPhil,[b] Norman Stockbridge, MD, PhD,[c] Thomas R. Fleming, PhD,[d] Robert Temple, MD,[c] Robert M. Califf, MD,[a] Stuart J. Connolly, MD,[e] Lars Wallentin, MD, PhD,[f] and Christopher B. Granger, MD[a] Participants in the Duke Clinical Research Institute/ American Heart Journal Expert Meeting on Antithrombotic Drug Development for Atrial Fibrillation

Durham, NC; Rochester, MN; Silver Spring, MD; Seattle, WA; Hamilton, Ontario, Canada; and Uppsala, Sweden

Am Heart J 2008;155:829-40



The RRR of warfarin compared with placebo in these trials using a random effects model was 0.36 (95% CI 0.24-0.53), such that the inverse of the upper boundary (ie, control compared with warfarin) is 1.88 (1/0.53). To establish that at least half of the warfarin effect is preserved, the noninferiority margin is 1.88 or 1.38 (ie, the margin is the midpoint between 1.0 and 1.88 on a log scale rather than linear scale because the primary parameter estimated is the logarithm of the relative risk).

Phase III Non-Inferiority Study of Cabazitaxel 20 mg/m^2 versus Cabazitaxel 25 mg/m^2 in Patients with Metastatic Castration-Resistant Prostate Cancer Previously Treated with Docetaxel (PROSELICA)

Johann de Bono,[1] Anne-Claire Hardy-Bessard,[2] Choung Soo Kim,[3] Lajos Geczi,[4] Daniel Ford,[5] Loic Mourey,[6] Joan Carles,[7] Phillip Parente,[8] Albert Font,[9] Gabriel Kacso,[10] Mustapha Chadjaa,[11] Wenping Zhang,[12] John Bernard,[13] Mario Eisenberger[14]

[1]Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, Sutton, UK; [2]Centre Armoricain d'Oncologie, CARIO, Plérin, France; [3]Asan Medical Center, Seoul, South Korea; [4]National Institute of Oncology, Budapest, Hungary; [5]City Hospital, Cancer Centre Queen Elizabeth Hospital, Birmingham, UK; [6]Institut Claudius Regaud, IUCT-O, Toulouse, France; [7]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [8]Eastern Health Clinical School, Monash University, Box Hill Hospital, Australia; [9]Institut Català d'Oncologia, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [10]Amethyst Radiotherapy Center, Cluj, Romania; [11]Sanofi, Vitry-sur-Seine, France; [12]Sanofi Genzyme, Bridgewater, NJ, USA; [13]Sanofi Genzyme, Cambridge, MA, USA; [14]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Johann de Bono

PROSELICA: Non-inferiority Design

- To test if the 95% OS HR CI of CBZ 20 and CBZ 25 are within the predefined parameters requested by the FDA
- The basic hypothesis is that CBZ 20 “maintains at least 50% of the OS benefit of CBZ 25 relative to mitoxantrone observed on the TROPIC study”
- To claim non-inferiority with 95% confidence level in the final analysis, the upper-bound CI of HR for CBZ 20 versus CBZ 25 could not exceed 1.214 under one-sided 98.89% confidence level after being adjusted for the interim analyses

Some essential considerations in the design and conduct of non-inferiority trials

Thomas R Fleming[a,b], *Katherine Odem-Davis*[a,b], *Mark D Rothmann*[c] *and Yuan Li Shen*[c]

Clinical Trials 2011; **8**: 432–439

Irregularities in quality of the conduct of the non-inferiority trial induce increased risk of both bias and variability.

While such irregularities are of concern in superiority trials, they are even more problematic in a non-inferiority trial since they often dilute the sensitivity to true differences between the experimental intervention and Standard regimens, leading to an increased risk of falsely declaring non-inferiority in settings where the test treatment truly is clinically inferior to Standard.

Studi di non-inferiorità:
Analisi ITT *Vs* analisi PP

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use
London, 27 July 2000 CPMP/EWP/482/99

IV.2.3 Choice of analysis set

In a superiority trial the full analysis set, based on the ITT (intention-to-treat) principle, is the analysis set of choice, with appropriate support provided by the PP (per protocol) analysis set. In a non-inferiority trial the full analysis set and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation.

Guidance for Industry
Non-Inferiority Clinical Trials

March 2010
Clinical/Medical

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)

Although an "as-treated" analysis is therefore often suggested as the primary analysis for NI studies, there are also significant concerns with the possibility of informative censoring in an as-treated analysis. It is therefore important to conduct both ITT and as-treated analyses in NI studies.
Differences in results using the two analyses will need close examination.

1. Riflettete da soli per 10 min. e compilate il form →
2. Confrontatevi con i Colleghi del Vostro tavolo per 15 min., declinate un W^3 condiviso e delegate un portavoce
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso

RIFLESSIONI E SINTESI
sui temi oggetto del Corso

WHAT?
Partendo da quanto ascoltato, seleziono quanto ritengo più importante (almeno due argomenti):

SO WHAT?
Il fatto che io abbia ritenuto alcuni argomenti più importanti è perché per me hanno un particolare significato. Quindi:

NOW WHAT?
Quali azioni potrei pensare di intraprendere in conseguenza di quanto sopra: