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How to evaluate medications in Multiple Sclerosis when placebo controlled RCTs are not feasible

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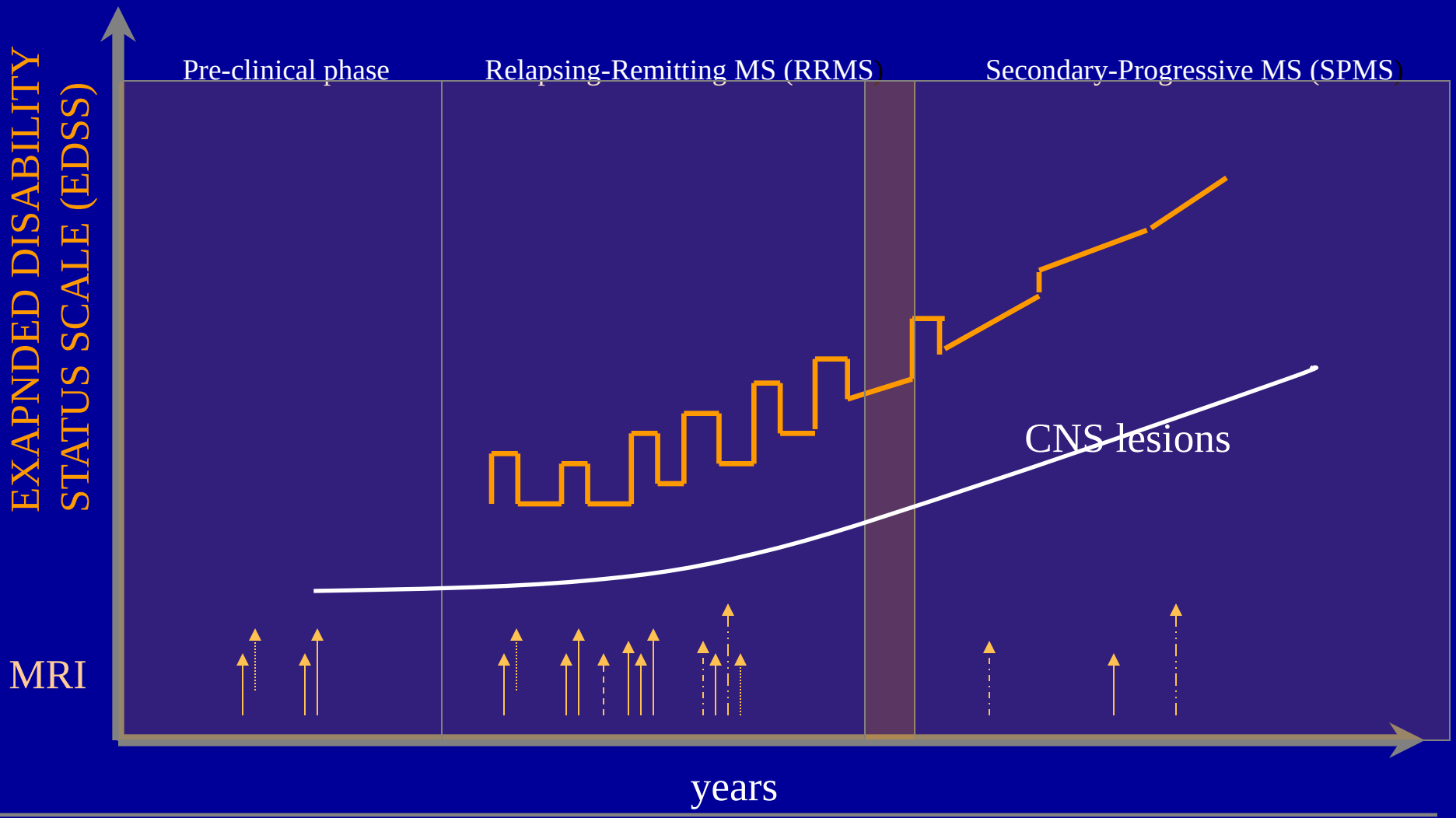
EMA, London October 2013

outlines

- Needs to be met in MS
- Comparative clinical trials
- Non-inferiority design

MS course: relation between clinical and magnetic resonance imaging (MRI) measures



Background

- In RR MS Disease Modifying Treatments (DMT), effective on clinically relevant outcome measures are available and approved.

- Efficacy or safety and therefore Therapeutic Index (TI: efficacy/safety) is variable and for each DMT is not optimal

- Clinical needs other than efficacy, not optimally met by these DMTs, are:
  - safety
  - patient compliance
  - administration convenience
  - costs

In MS clinical needs different from efficacy often unmet

- In the presence of DMTs approved for MS, new treatments are still worth to be developed for this indication, aiming also to superiority of pharmacological characteristics other that efficacy as:
  - safety
  - patient compliance
  - administration convenience
  - costs

Condition for aiming to improvements on characteristics different from efficacy

- In MS, if new DMTs (or new formualtion of already approved DMTs) with better pharmacological characteristics will be developed, the efficacy must be at least equivalent to that of the currenly available treatments

Example

- New Interferon Beta 1a, IM, formulation (pegylated, allows less frequent injections): evaluated in a short RCT vs placebo showing efficacy similar to the old formulation (same molecule) administrated weekly (AAN 2013; ECTRIMS 2013)

  Head to head comparison with the approved formulation lacking;

  – In this case superiority not hypothesized: could non inferiority design be recommended?

Comparative trias design alternative to superiority

- AIM : to prove that efficacy of an experimental treatment (S) is at least **equivalent** to that of a reference treatment (T) that acts as control;

- Needed to compare medications differing only as for characteristics other than efficacy

- Equivalence :
  - when the two treatment under study exert indistinguishable activity on the most clinically relevant outcome measures, in spite of some variability
- Equivalence cannot be proved as for:
  - $\delta = 0, n = \infty$
- Non-inferiority with respect to a predetermined difference can be proved

Non inferiority design

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Recommended for Adoption
at Step 4 of the ICH Process
on 5 February 1998
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS
E10

Recommended for Adoption
at Step 4 of the ICH Process
on 20 July 2000
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Reporting of Noninferiority and Equivalence Randomized Trials

An Extension of the CONSORT Statement

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The CONSORT (Consolidated Standards of Reporting Trials) Statement, including a checklist and a flow diagram, was developed to help authors improve their reporting of randomized controlled trials. Its primary focus was on individually randomized trials with 2 parallel groups that assess the possible superiority of one treatment compared with another but is now being extended to other trial designs. Noninferiority and equivalence trials have methodological features that differ from superiority trials and present par-

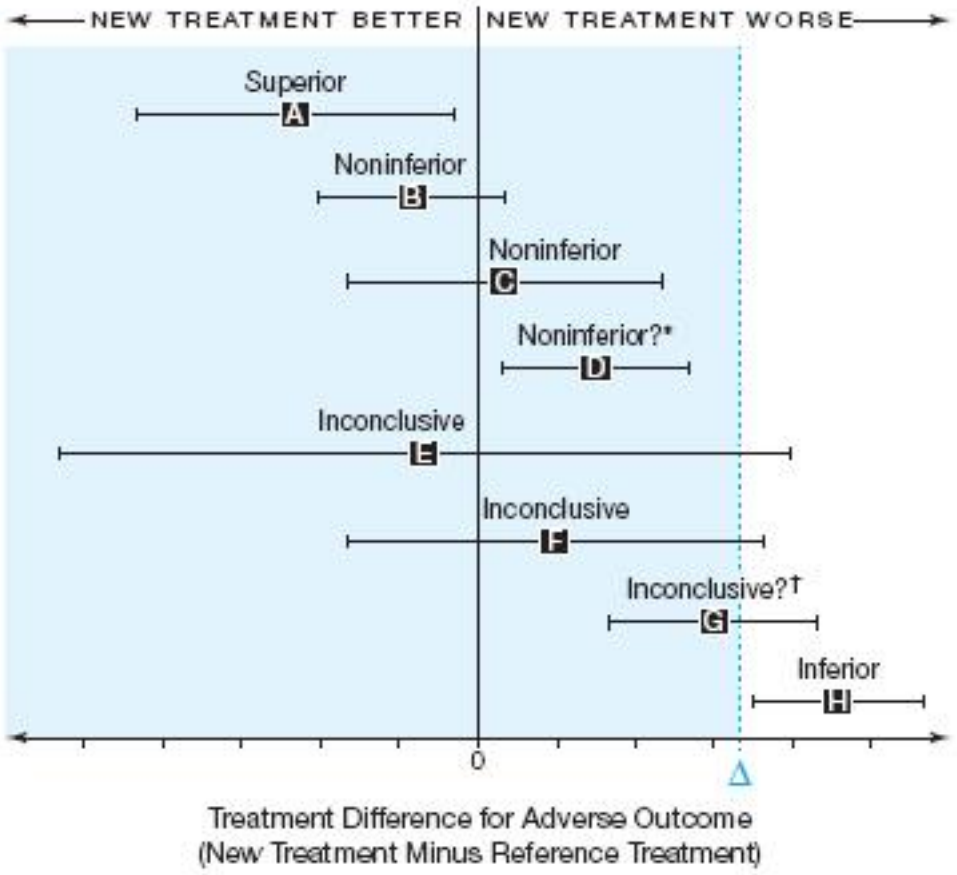
Non inferiority design represents a virtual comparison with Placebo of a given treatment S

- Assumptions:
  - If the efficacy of an experimental treatment (S) is superior to that of a reference treatment (T) known to be superior to placebo, also S efficacy is superior to placebo;
  - Therefore efficacy of S would have been superior to Placebo, if this intervention would have been included in the trial

- Conditions:
  - Previous phase II or III placebo controlled RCTs consistent among them, allowing precise evaluation of :
    - the dimensions of the effect: $E = S / P$ $(S - P)$
  - distribution and frequency of the end-point(s), in the same patient population has been reliably estimated

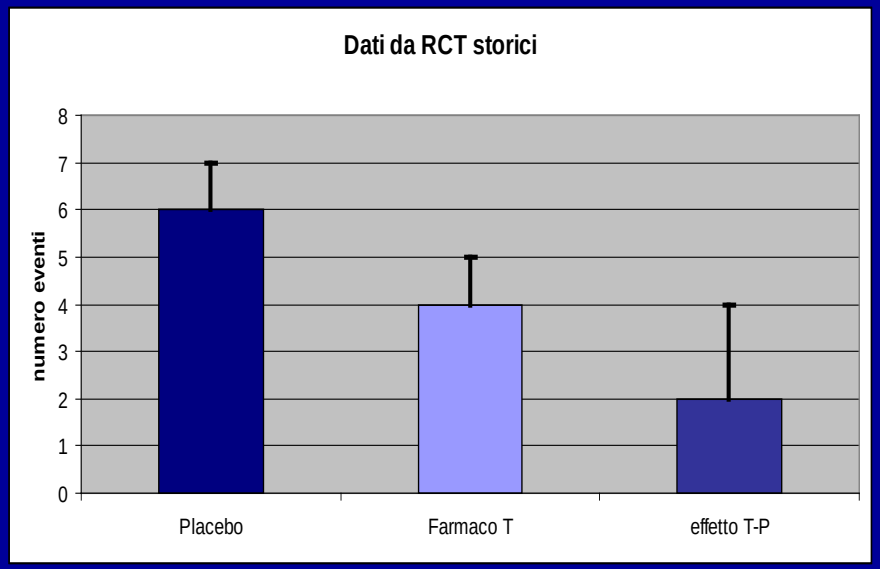
Method: non-inferiority

Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



- Treatment S is non-inferior to control treatment T if the lower CI (one tail) of its effect, falls within a predefined margin M named “non-inferiority margin”
- M value:
  - arbitrary
  - clinically meaning ful
  - predefined

Non inferiority margin M estimate



- Calculation:
  - clinically meaningful fraction of the Effect (E) of the reference treatment (T) vs Placebo resulting from high quality phase II or III trials.
    - M= $\frac{1}{x} E_{T/P}$

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

London, 27 July 2005
Doc. Ref. EMEA/CPMP/EWP/2158/99

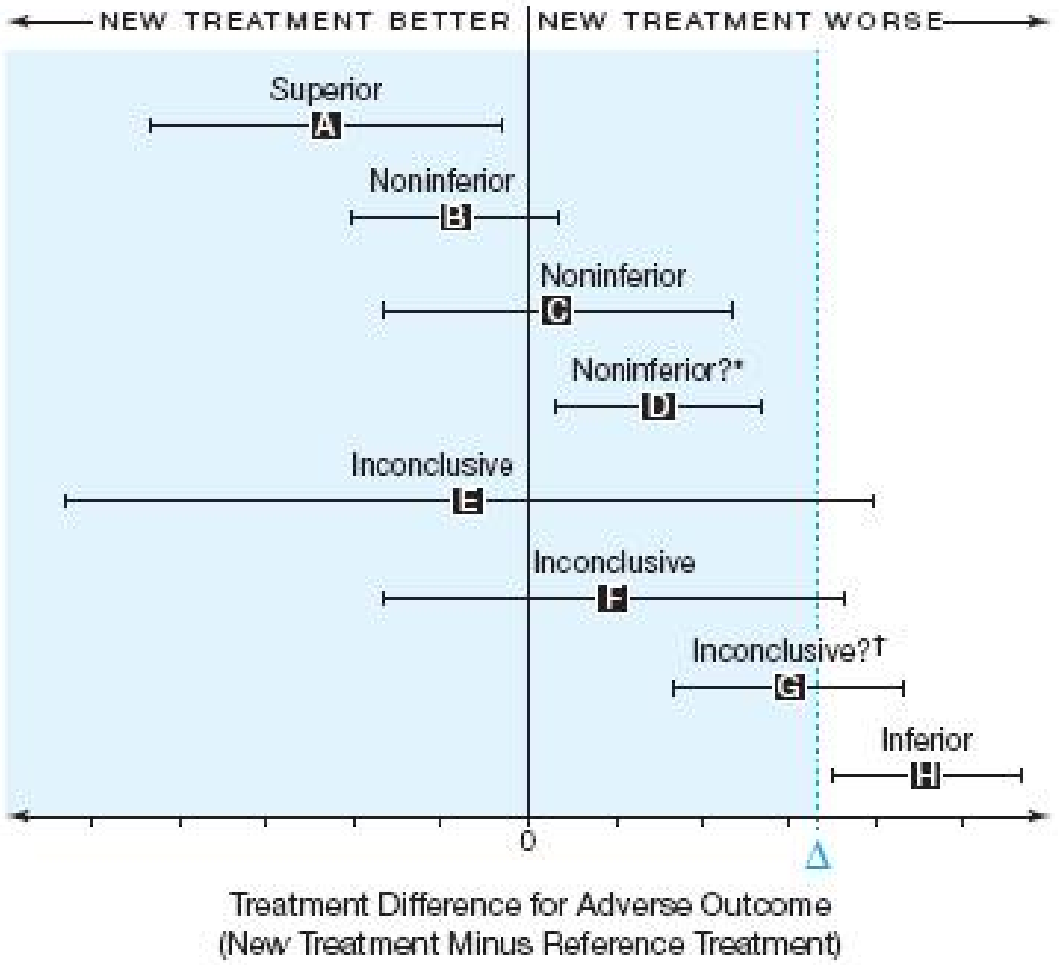
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN

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

The treatment S is non-inferior when its effect vs the comparator T results within a predefined margin named “non-inferiority margin”

Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



The null hypothesis in comparative head to head RCTs

- Comparing treatments with different efficacy, superiority of one treatment is assumed:
  - the null hypothesis is no difference and the alternative is difference
- Comparing treatments with similar efficacy, equivalence is not assumed;
  - the null hypothesis is difference and the alternative is no difference

- Superiority trials:
  - null hypothesis:
    - $H_0 = m_1 / m_2 = 1$; or $H_0 = m_1 - m_2 = 0$
  - alternative hypothesis:
    - $H_1 = m_1 - m_2 > \delta$; or $H_1 = m_1 - m_2 > \delta$

  Sample size is inversely proportional to a predefined δ

- Equivalence ($\delta = 0$):
  - not feasible because $n = \infty$.

- Non inferiority trials :
  - null hypothesis:
    - $H_1 = m_1 / m_2 > \delta$: or $H_1 = m_1 - m_2 > \delta$
  - alternative hypothesis:
    - $H_0 = m_1 / m_2 = 1$; or $H_0 = m_1 - m_2 = 0$

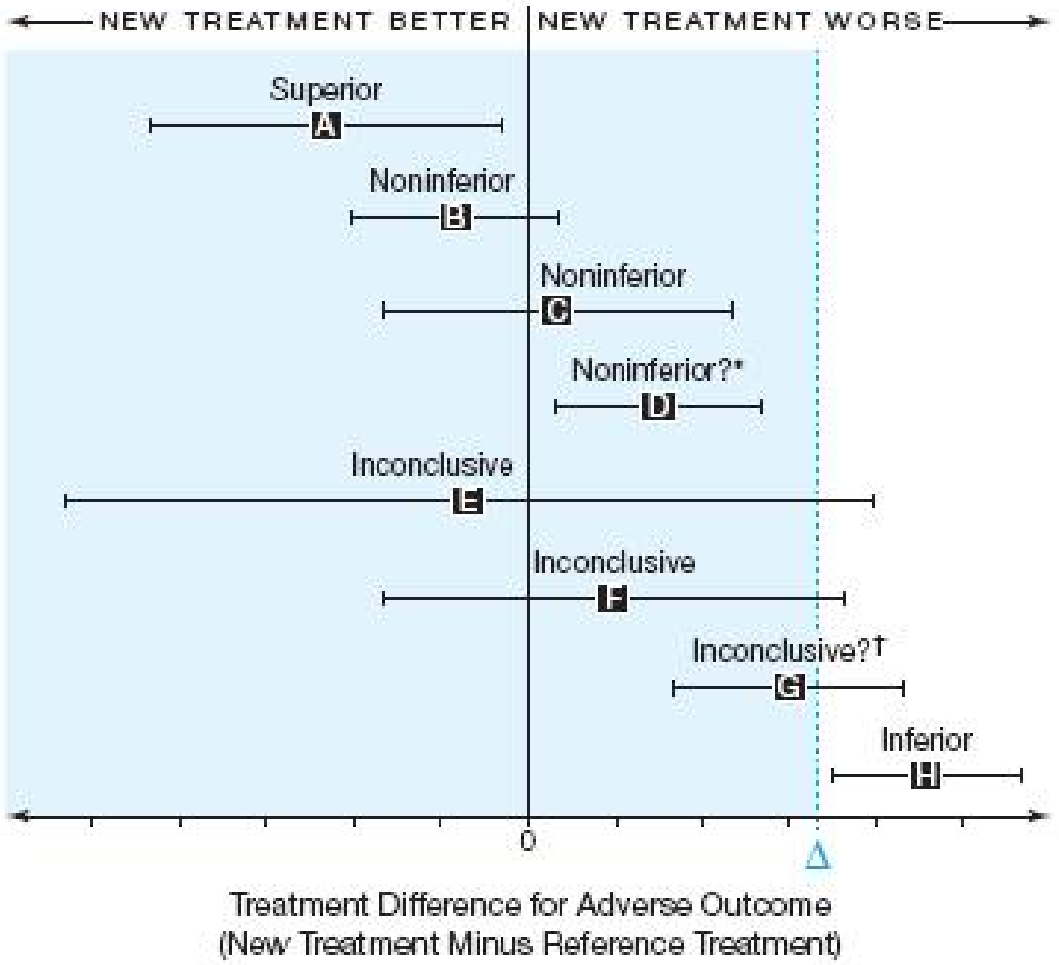
  Sample size is inversely proportional to a predefined δ

How to compare efficacy between treatments if no or little difference is assumed?

$$n = 2\left[\frac{(q-k)}{\delta} sd\right]^2$$

The treatment S is non-inferior when its effect vs the comparator T results included within a predefined margin named “non-inferiority margin”

Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



CAVEAT: M estimate

- M value is clinically meaningful if M is established through a reliable estimation of the T effect size vs placebo
- For this purpose the following conditions must be fulfilled:
  - different high quality reference trials that evaluated T efficacy vs placebo must be available
  - their results must be consistent
  - the effect size vs placebo must be large enough to allow establishment of a clinically meaningful size of M
  - The patient population and therefore the dimensions of the outcome measure selected as the primary end point must be stable along time

IFN efficacy vs. placebo in reference studies

TRIAL treatment		**Betaferon (BIFN 1b, 1993)**			**PRISMS (BIFN 1a 44, 1997)**			**PRISMS (BIFN 1 a 22, 1997)**			
		n	relapse n./2y		n	relapse n./2y		n	relapse n./2y		
B IFN		122	1.68		187	1.73		189	1,82		1.74
Placebo		155	2.54		184	2.56		184	2,56		2,55
delta			0,86			0,83			0,74		0.81
ratio			1,51			1,48			1,40		1,46

relapse rate ratio Placebo/βIFNs = 1.46

Statistics

Non-inferiority

- 1.46, the relapse rate ratio between the placebo and the βIFNs group, detected in 2 pivotal historical trials (PRISMS; Betaferon)

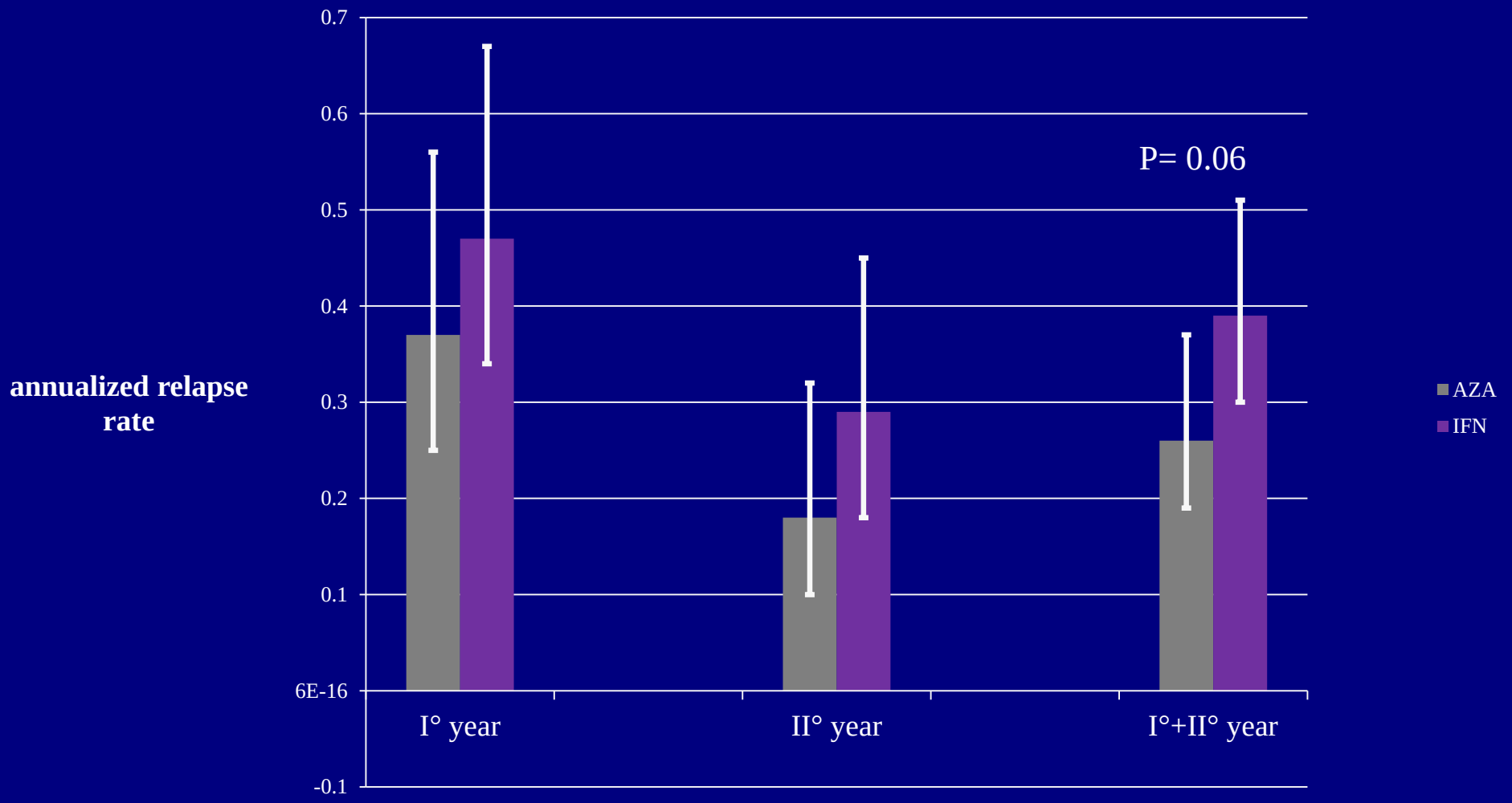
- non inferiority margin M a priori established, as 50% of the excess to 1.0 (= 1.23)

- Treatment S will be considered non-inferior to βIFNs if the 95% C.I (one side) of the ratio between relapse rates in the S group and in the βIFNs group will be < 1.23

CAVEAT: protocol violations

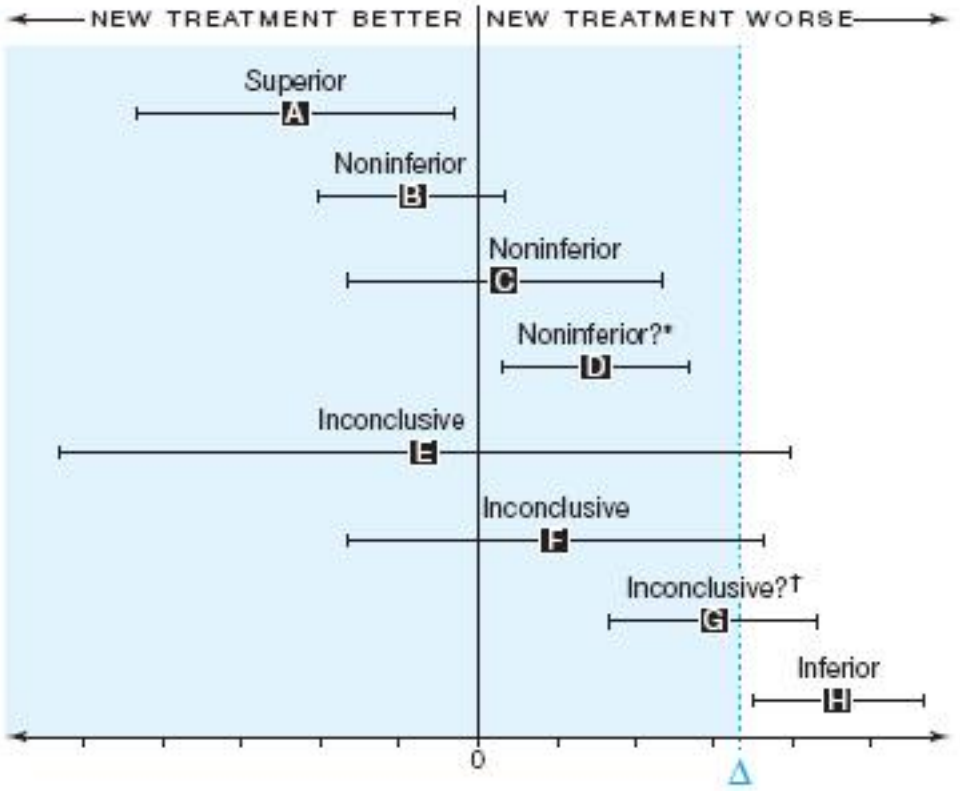
- If none of the patients included, assume the assigned drug, non inferiority is granted
- Both intention to treat (ITT) and per protocol (PP) analysis must be carried out and must give equivalent results.

Effect on Relapse Rate over 2 years

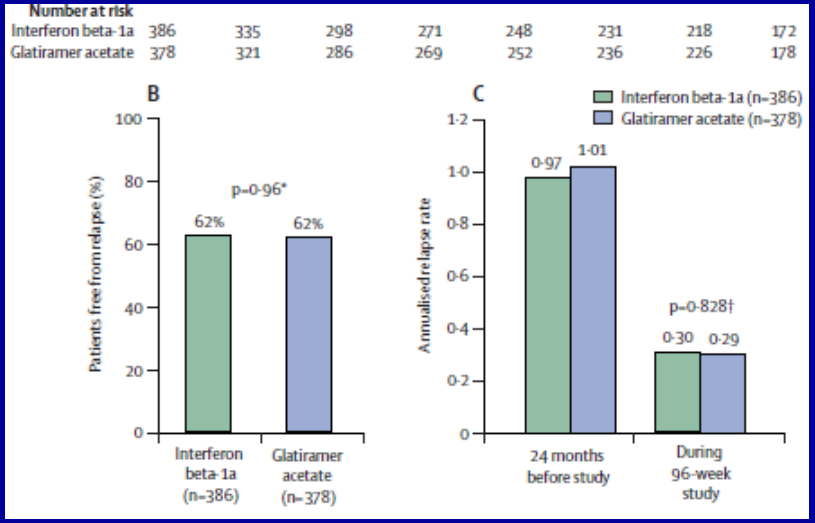


RR: between A and B scenario

Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



Head to head Comparison of a Beta Interferon 1a and Copaxon (Mikol et al., 2008)



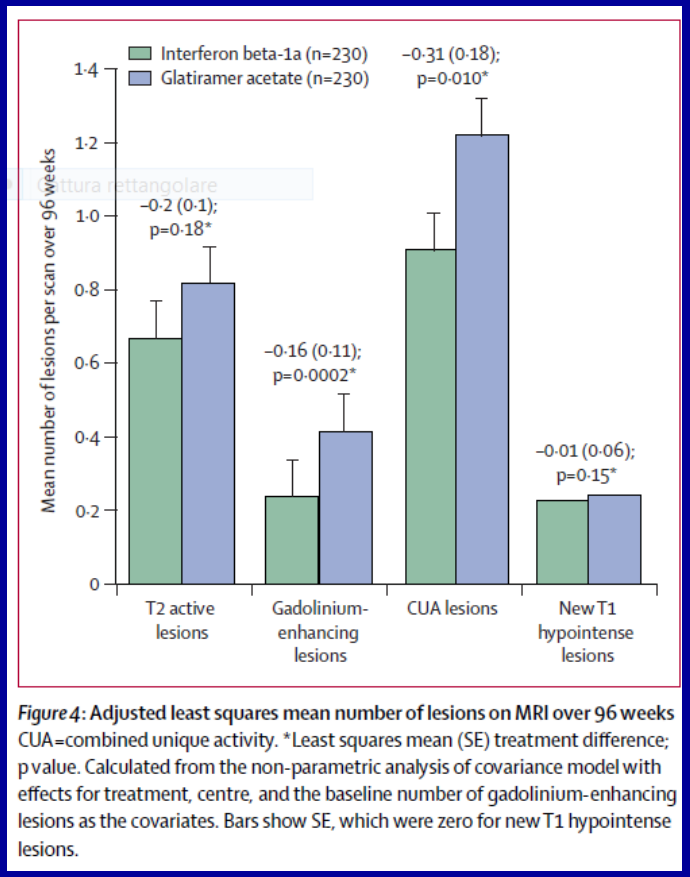


Figure 4: **Adjusted least squares mean number of lesions on MRI over 96 weeks**
CUA=combined unique activity. *Least squares mean (SE) treatment difference; p value. Calculated from the non-parametric analysis of covariance model with effects for treatment, centre, and the baseline number of gadolinium-enhancing lesions as the covariates. Bars show SE, which were zero for new T1 hypointense lesions.

Summary

- In RRMS comparative trial will be increasingly used for developing new medications
- Some of them will not aim to evaluate superiority of efficacy but of other pharmacological characteristics
- For this purpose, high quality well conducted non inferiorty design may represent a reasonable option

Thanks for your attention

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