Design strategies to minimise the use of placebo in MS clinical trials

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Study design strategies

- Active controlled trials:

  both arms receive an active treatment

- Surrogate endpoints:

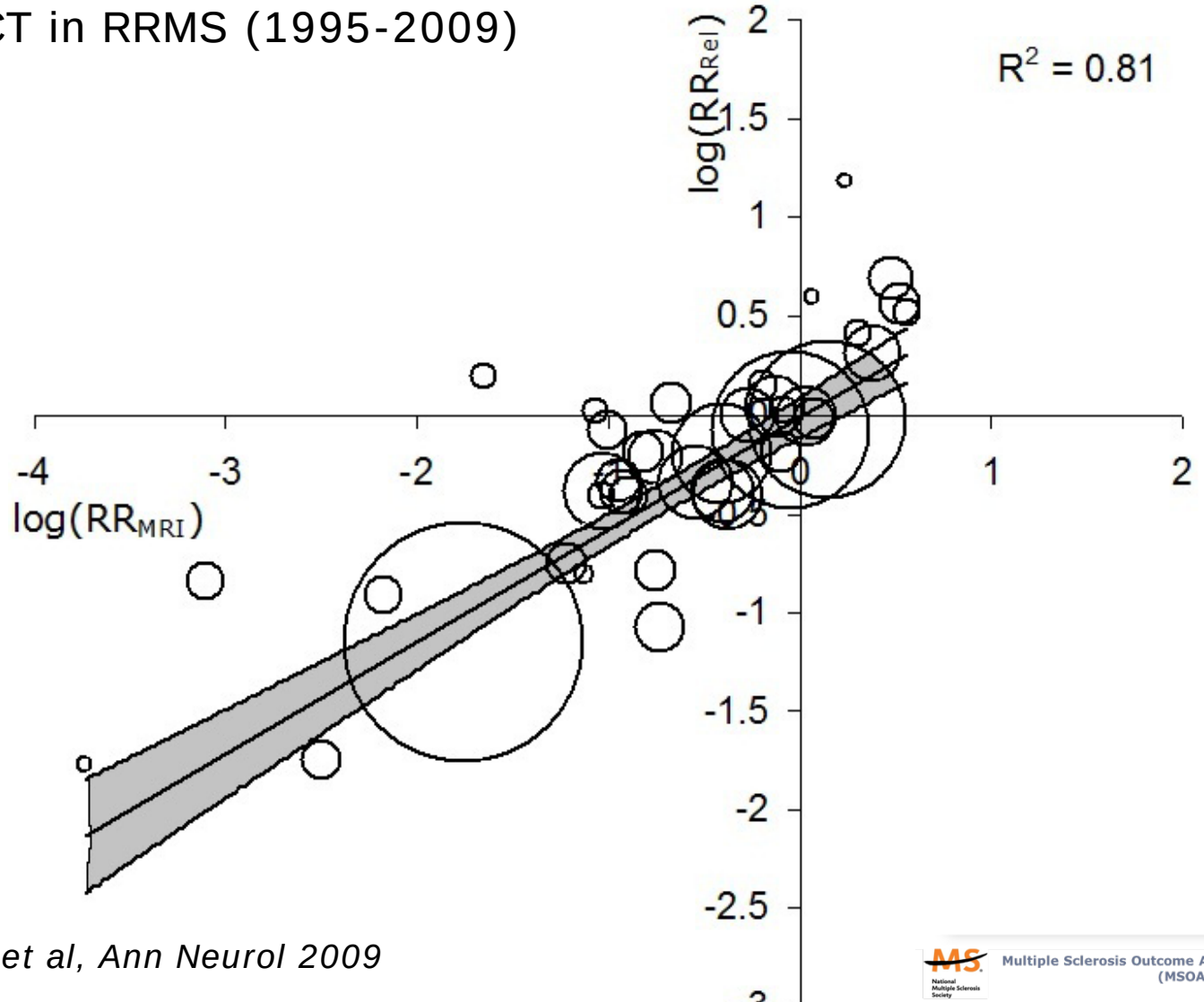
  their use minimise the number of subjects and the time of exposure to placebo

Surrogate endpoints- MRI markers

Line 354 EMA Guidelines: …So far, MRI measurements ***have not been proven*** *to be a reasonably validated surrogate endpoint of the clinical outcomes and are, therefore,* ***not acceptable*** *as a primary endpoint in pivotal studies…*

MRI markers as a surrogate for relapses

23 RCT in RRMS (1995-2009)



Sormani et al, Ann Neurol 2009

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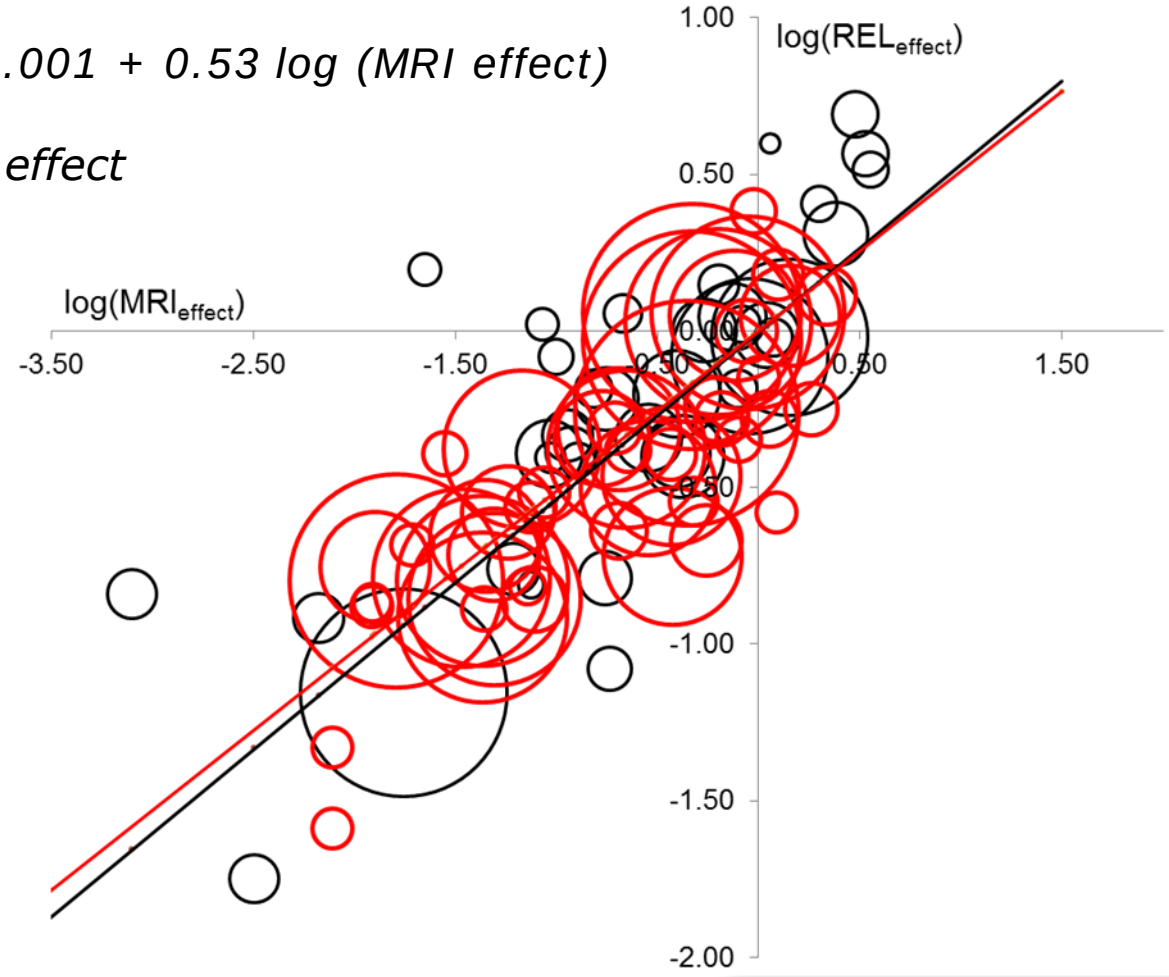
MRI markers as a surrogate for relapses

31 RCT in RRMS (2009-2013)

$R^2 = 0.76$

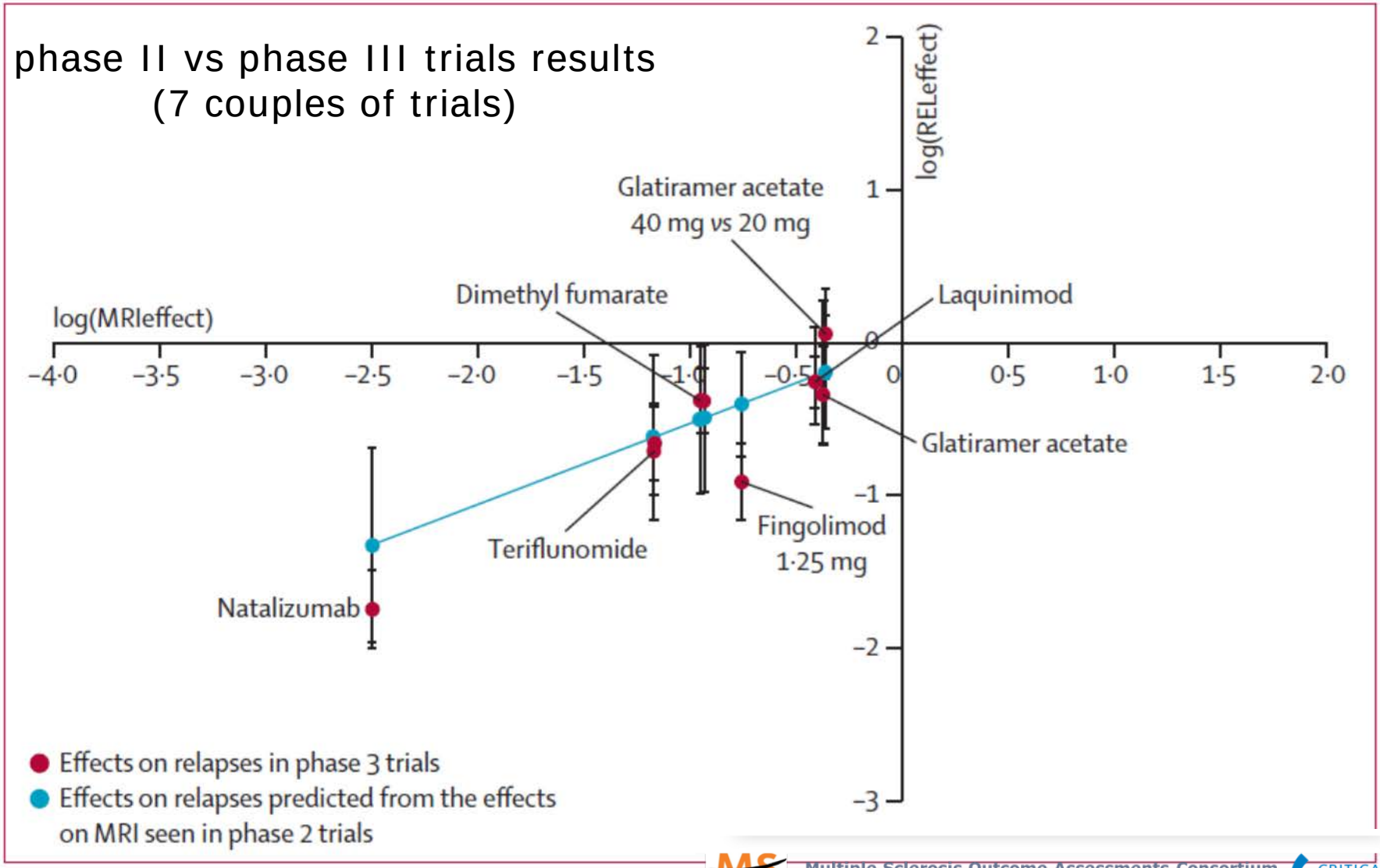
log(REL effect) = 0.001 + 0.53 log (MRI effect)

REL effect ~√ MRI effect



Sormani et al, Lancet Neurol 2013

MRI markers as a surrogate for relapses



Sormani and Bruzzi, Lancet Neurol 2013

MRI markers as a surrogate for relapses

The paradigm MRI lesions-relapses seems to be valid trough a broad range of treatments.

This observation supports the use of **MRI lesions** as a surrogate for **relapses**

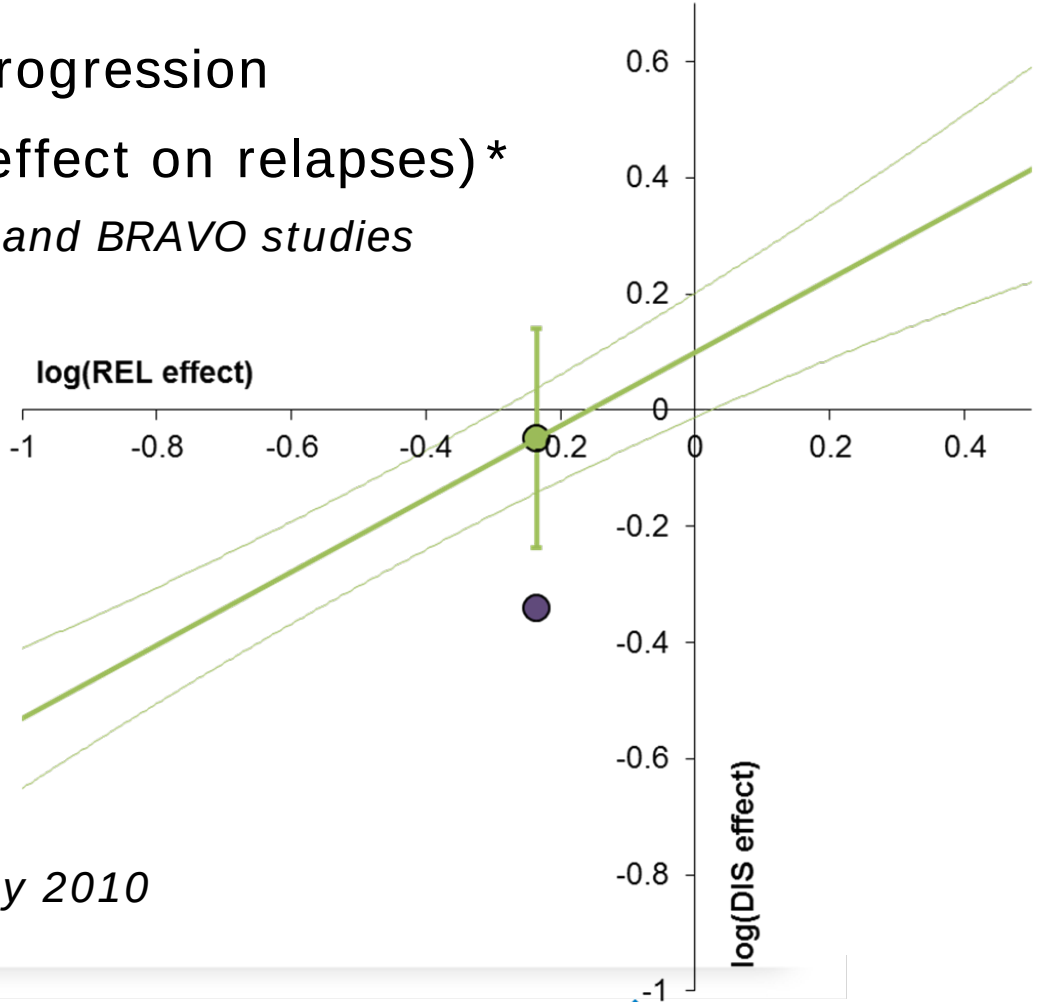
The relationship MRI lesions-disability is less predictable and was not assessed by this analysis

Example – Relapses-Disability

Effect on disability progression

(observed vs predicted from effect on relapses)*

Pooled analysis of the ALLEGRO and BRAVO studies



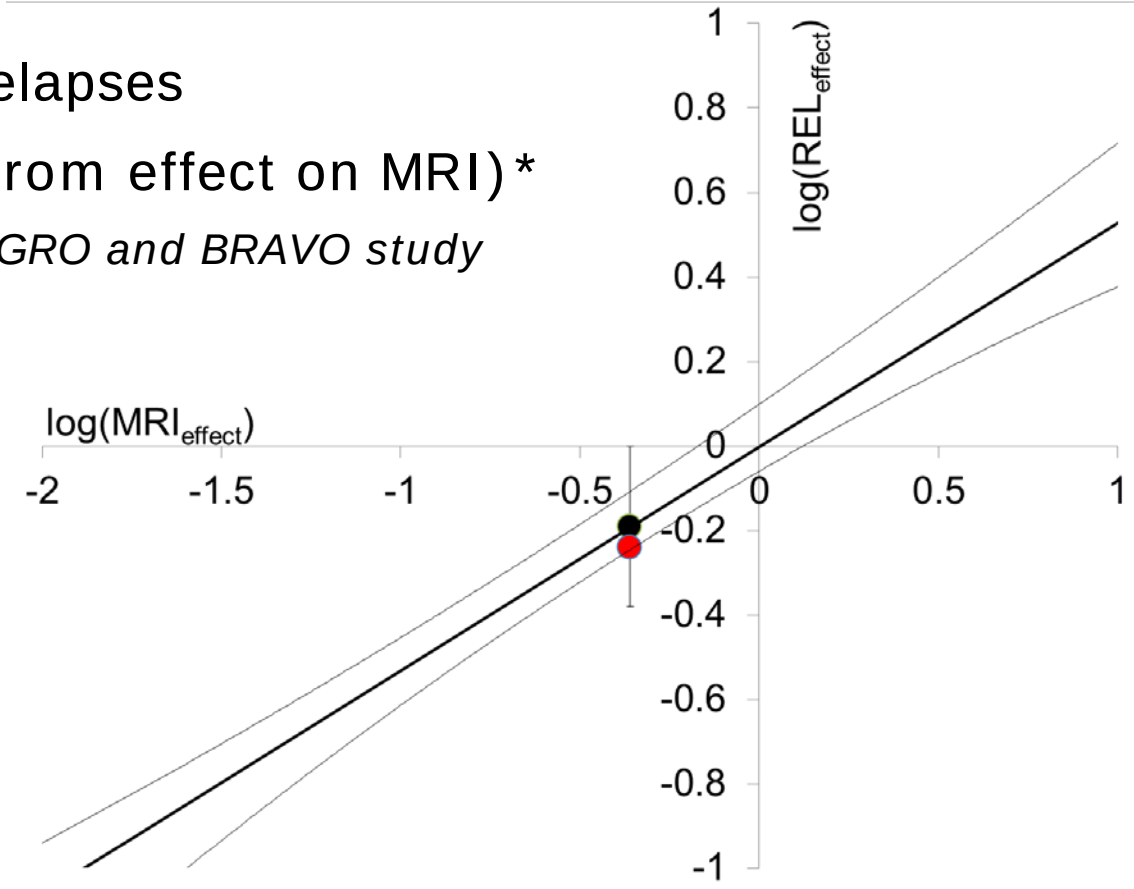
**according to Sormani et al Neurology 2010*
Sormani et al, ECTRIMS 2013

Example – MRI markers-Relapses

Effect on relapses

(observed vs predicted from effect on MRI)*

Pooled analysis of the ALLEGRO and BRAVO study



The observed effect on relapses was the one predicted by the observed effect on MRI

**according to Sormani et al Lancet Neurol 2013*

Surrogate endpoints – MRI markers

The paradigm MRI lesions-relapses seems to be valid trough a broad range of treatments. MRI lesions are a good surrogate for relapses in MS.

The use of MRI endpoints in pivotal trials must be seen with more flexibility

More flexibility?

1. In the design of trials for testing the efficacy of drugs on relapses, at least for drugs with known mechanisms of action.

    - Example: Biosimilars, peg-IFN

2. For testing the efficacy of drugs already approved for adults in pediatric populations
3. For assay sensitivity in equivalence or non-inferiority trials
4. Adaptive trials

More flexibility? - Adaptive designs

Biometrics 68, 258–267
March 2012

DOI: 10.1111/j.1541-0420.2011.01647.x

Bayesian Adaptive Trial Design for a Newly Validated Surrogate Endpoint

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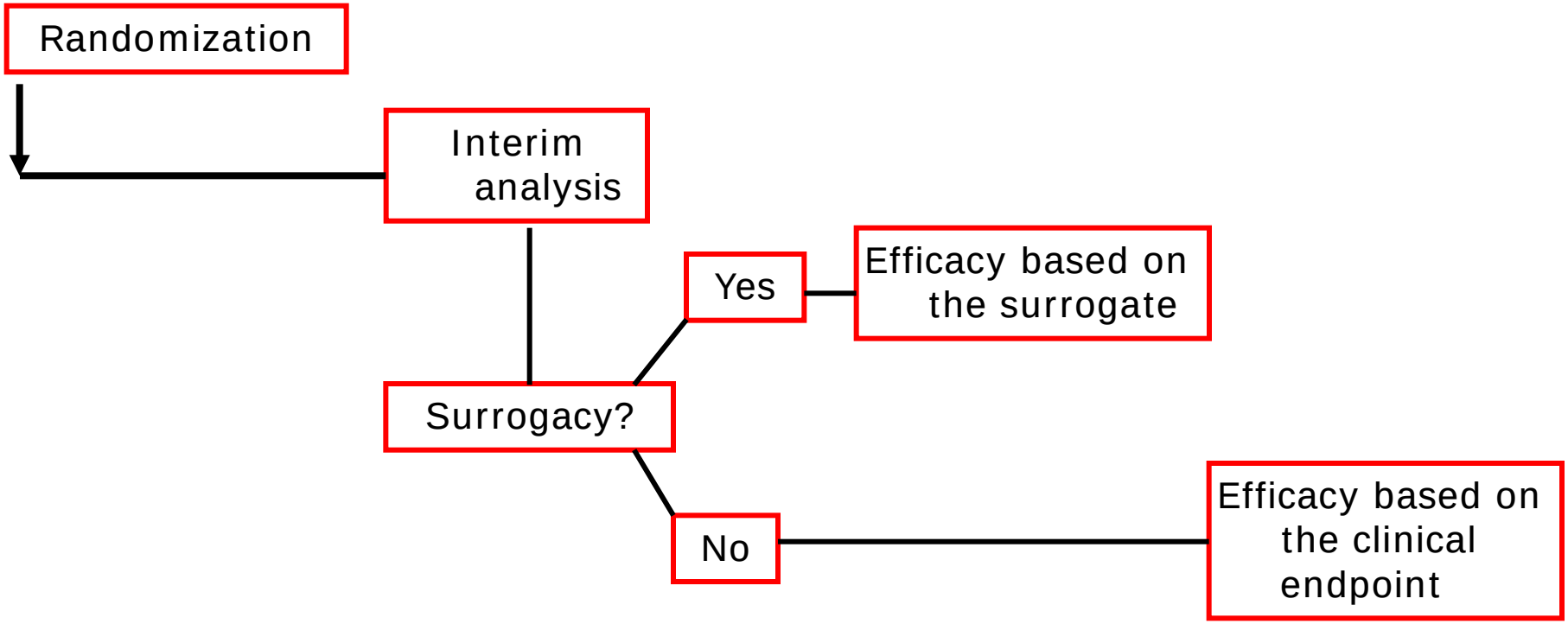
Surrogate endpoints + adaptive design

If we have a newly validated surrogate endpoint (MRI in specific situations for MS)



MRI endpoints – study design

- A phase III trial with MRI as the primary endpoint should not be based only on the statistical significance of the effect on MRI
- Rather, the effect on MRI should be precise enough to guarantee a predicted effect on relapses which is clinically meaningful

Conclusions – more flexibility

*Line 354 EMA Guidelines: …So far, MRI measurements **have not been proven** to be a reasonably validated surrogate endpoint of the clinical outcomes and are, therefore, **not acceptable** as a primary endpoint in pivotal studies…*

*So far, MRI measurements **have been proven** to be a reasonably validated surrogate endpoint of **relapses,** while have not be proven to be a surrogate of disability accumulation. Therefore, their use as a primary endpoint in pivotal studies can be considered only in very specific situations.*

Conclusions – more flexibility

The MSOAC is working to the definition of a new clinical outcome for the assessment of drug efficacy in MS.

All the consortium members encourage regulatory agencies to leave the guidance open to the introduction of newer endpoints including an enhanced measure of disability in a few years.