An adaptive two-stage design for an early phase study of multiple biomarkers

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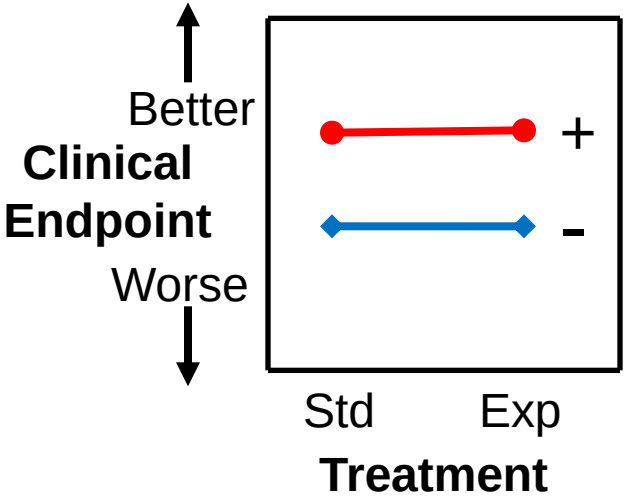
Outline:

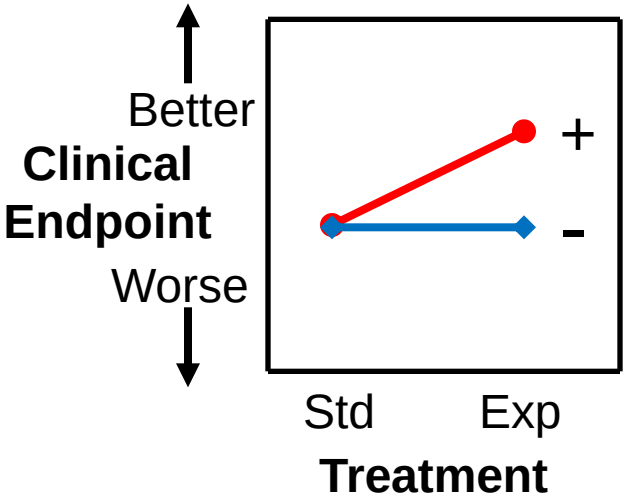
- What are biomarkers --- which design when?
- A two-stage study to inform a biomarker trial
- Considerations for primary care research

Biomarkers – classifications and uses



Prognostic:

- associated with **disease outcome**
  (not specific to treatment)
- risk assess (+,-) to stratify for any treatment



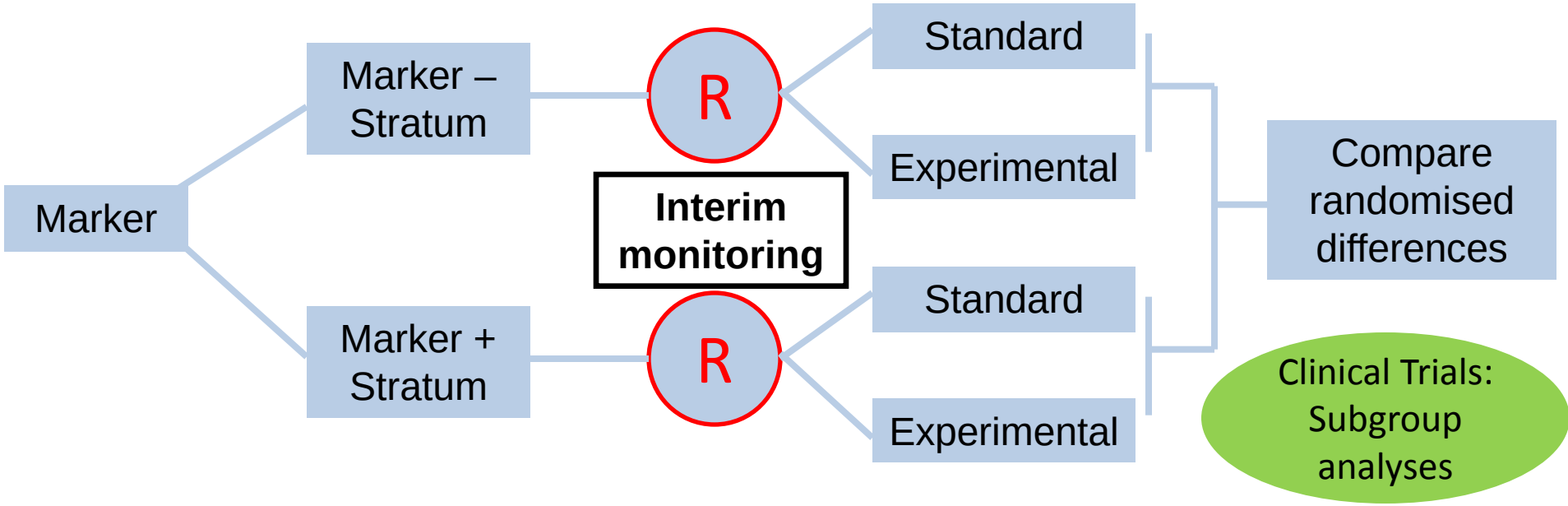
Predictive:

- associated with **treatment response**
- M+ benefit from experimental tmt
- individualise therapy
- personalised medicine

Biomarkers – roles in trials of various designs...

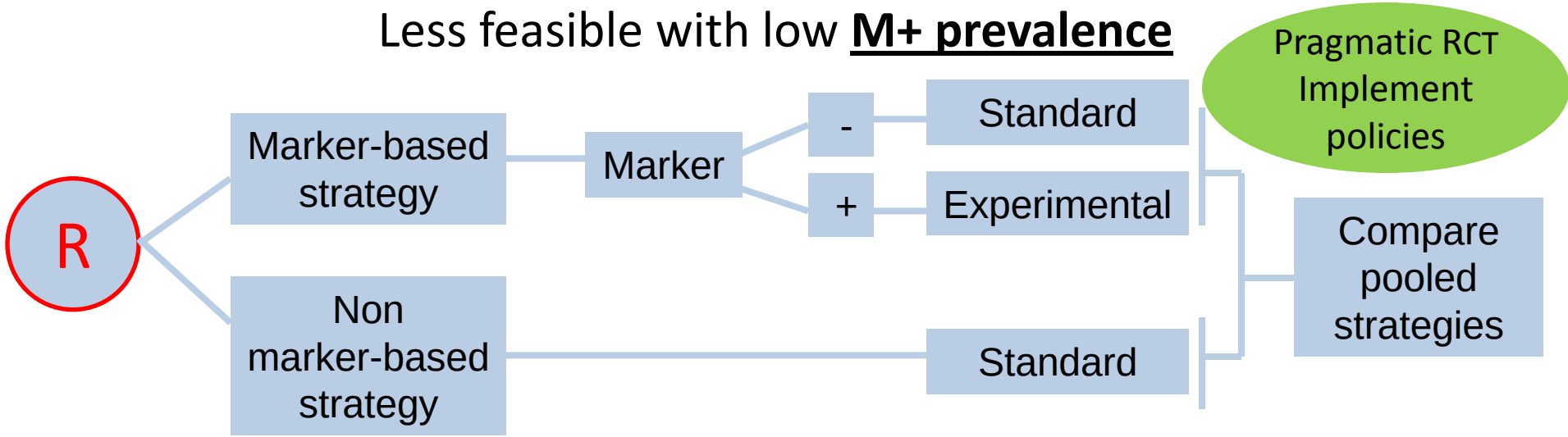
Biomarker-Stratified Design (Full specification)

Recommended when **preliminary evidence of effect** is less robust



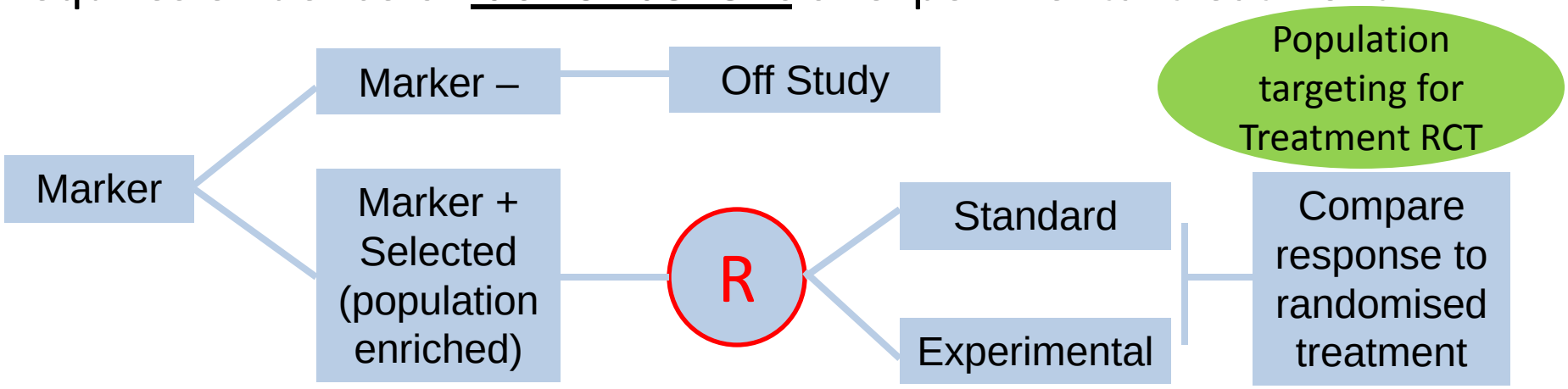
Biomarker-Strategy Design ("Usual care" b

Less feasible with low **M+ prevalence**



Enrichment Design (targeted/selected)

Requires evidence of **lack of benefit** of experimental treatment in M-



Choice of design depends on... evidence for a biomarker role...

- **quality** (reproducibility, validation –relevant, robust, accurate)
- **effect size** of marker-treatment relationship
- **lack of benefit** in M-
- **prevalence** of M+
- **finding** those effective ones from multiple biomarkers
- **practical limits** of sample size, cost, turnaround

'Combining ***scientific, clinical, statistical*** *and* ***ethical*** considerations

Requires early phase studies to <u>fill gaps</u> and <u>increase potential</u>

So what / References – biomarker trial design

Mandrekar SJ, Sargent DJ (2009) *J of Biopharmaceutical Statistics* 19:530-42
Clinical Trial **Designs** for **Predictive** Biomarker **Validation**:
One size does not fit all.

Mandrekar SJ, Sargent DJ (2009) *J Clin Oncol.* 27:4027 –34
Clinical trial designs for predictive **biomarker** validation:
theoretical considerations and **practical** challenges.

Freidlin B, McShane LM, Korn EL (2010) *J Natl Cancer Inst* 102:152 –60
Randomized Clinical **Trials** With Biomarkers: **Design** Issues.

Buyse M (2007) *Eur J Cancer Suppl.* 5:89 –95
Towards validation of **statistically reliable** biomarkers.

Zhou X, Liu S, Kim ES, Herbst RS, Lee JJ (2008) *Clin Trials*. 5:181-93
Bayesian **adaptive design** for **targeted therapy** development in lung cancer— a step toward **personalized medicine**.

The "client", the tal

Aim

Identify biomarkers specific to Psoriasis
that predict response from treatment singly
and in combination, sufficiently well
to inform a larger scale trial and given scarce resources

Basic design (Non-experimental)

Healthy controls + Controls with different skin condition
Psoriasis patients on treatment
Evaluation of biomarkers in all
Evaluation of treatment response in Psoriasis patients

'Alternative' Hypotheses

Biomarker distribution differs between patients & controls.
Response to treatment depends on biomarker.
Multiple biomarkers may predict and may usefully combine.
Useless biomarkers identifiable early in-study, saving resources

Example 1 –Rheumatoid Arthritis Study

Davis JM et al. Journal of Immunology 2010;184:7297-304.

Early RA group (n=25) / controls (n=15)

- develop immune response sc

But many variables / over-fitted model / abandoned methods

Need to improve **reproducibility** of score **to increase sample size**

Example 2 –Psoriasis proof of principle Study

Kagami S et al. Journal of Investigative Dermatology 2010;130:1373-83.

n=5 patients treated with infliximab (treatment)

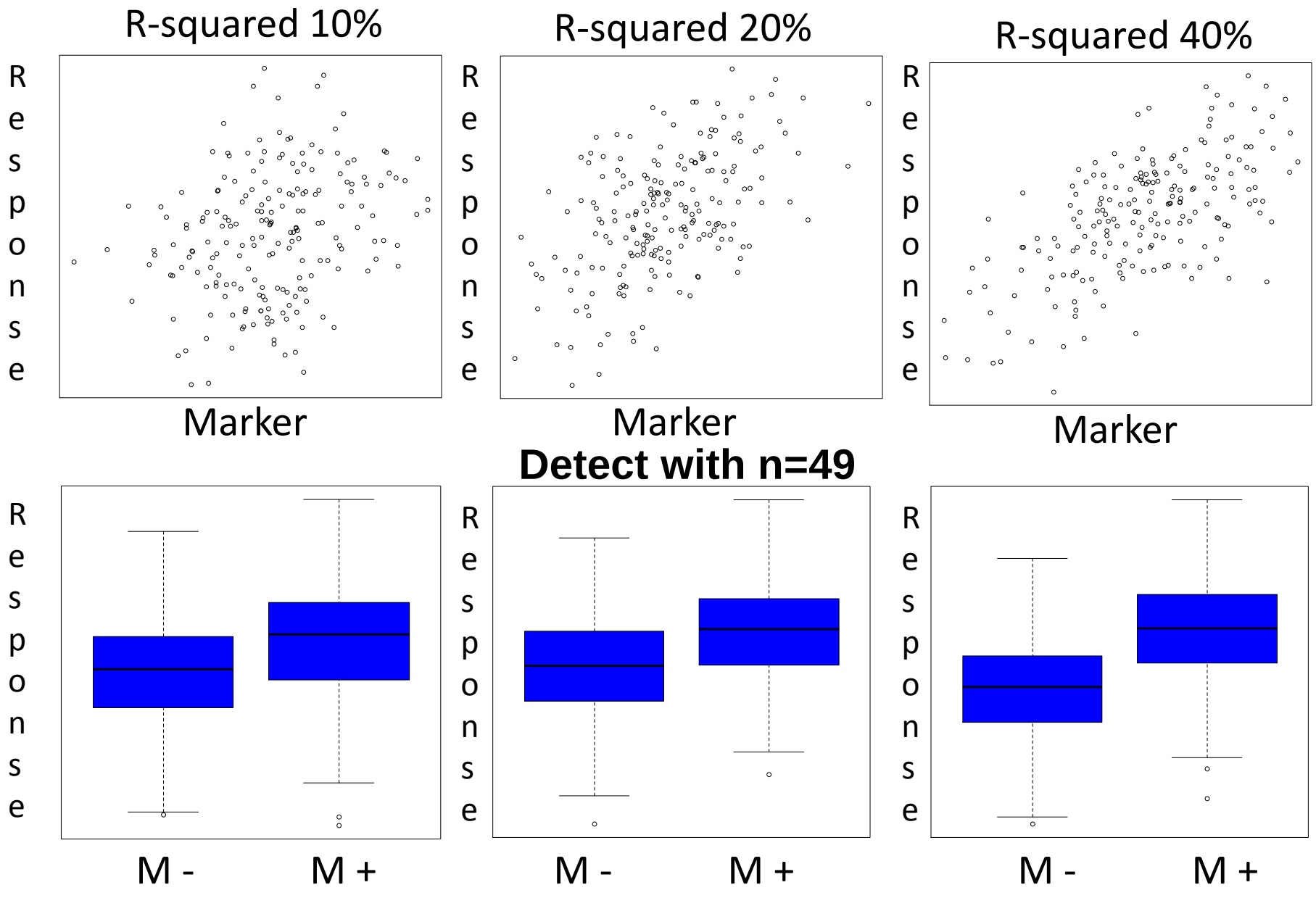
- decline in mean severity score (response)
- decreases in Th17 / Th1 cells (marker)

Assess patient-level *marker-response* in **larger** sample

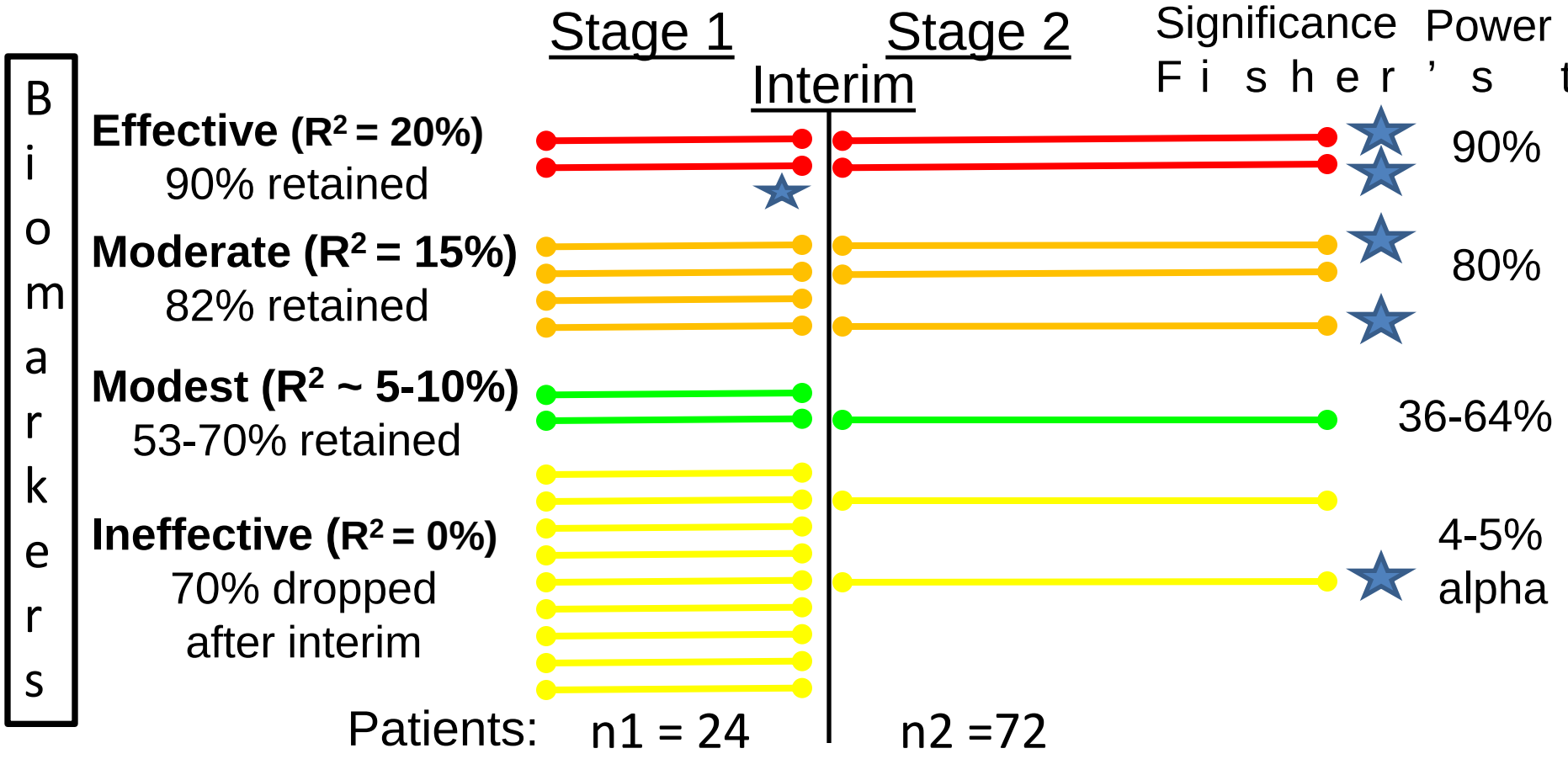
Consider **control** treatment to establish marker specific to infliximab

What effect size should be detectable?

(variation in treatment response explained by biomarker)



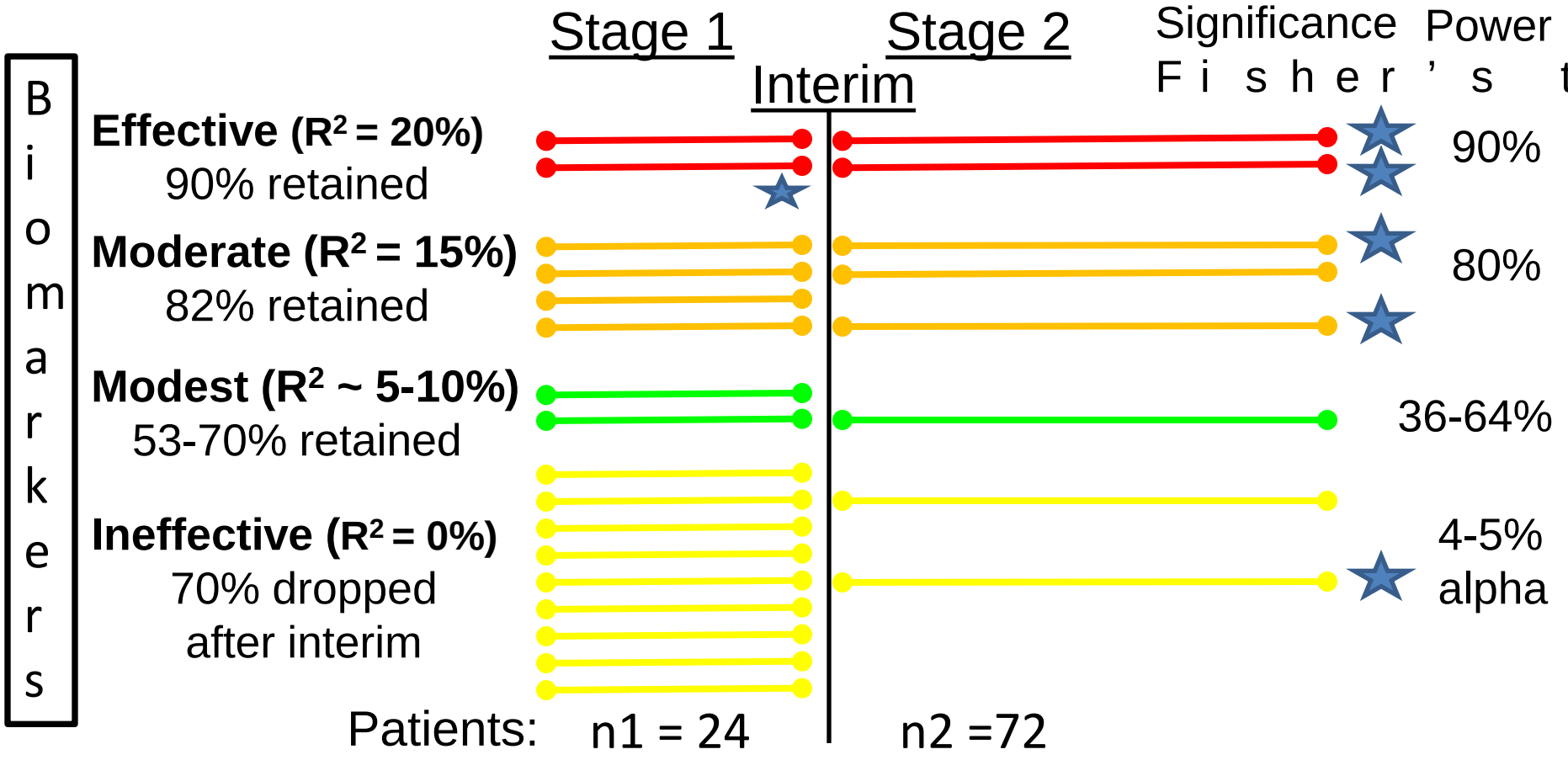
Alternatively: a 2-stage adaptive interim design



Bauer P, Kohne K Evaluation of experiments with adaptive interim analyses Biometrics 1994:50:1029-41

- early interim stopping: marker futility ($p > 0.3$; equivalent to $r^2<5\%$)
- additional "guarantee-" for markers retained
- larger sample (n2=72) with focused biomarkers to develop combination
- research into unbiased estimation of correlations and combinations

Alternatively: a 2-stage adaptive interim design



- power and alpha raised a litt
- under H1 - 1.2% of tests produce opposite signed correlations
  reduces power by 0.4%
- under H0 –reduce Type 1 error rate by 2%
  if reject when signs of stage correlations are opposite

Further work –Jack Bowden

MRC | Biostatistics Unit

- Extend unbiased estimation to correlation coefficient

- Compare strategies for developing biomarker combinations

- Incorporate biomarker cost

Bowden J, Glimm E (2008)
Unbiased Estimation of Selected Treatment Means in Two-Stage Trials.
Biometrical Journal 50:515 –27

Posch M, et al. (2005) Testing and estimation in flexible group sequential designs with adaptive treatment selection.
Statistics in Medicine 24:3697 –3714

Comparison with a primary care study

Two 2-stage studies	Clinical study to promote *biomarkers*	Primary care validation of *questions*
Adapt by dropping	Biomarker(s)	Question(s)
Outcome	Continuous – response on treatment	Binary – 'inherited' of conditions
Stage 1 patients	Quarter	Half
Interim rule Power	P>0.3 90%	P>0.15 95%
Re-combine data?	Yes	No; conditional

1. How can two stages offer value in early/late phases?
2. Is it feasible/appropriate to re-combine stage data?

Concluding points

Biomarker trials

"One size does not fit all"

Later design choice informed by role/characteristics of marker

Early phase studies increase potential to learn

- –which biomarkers / combination / prevalence
- –treatment specificity / effect size / which later phase design

Consider adaptive element

- – **cost-saving** on markers
- – **larger n** & **focus** 2nd stage efforts on promising biomarkers

Plan design and analysis together

- –to know the **effect size detectable**
- –with sample size based on **power/ability to detect**
- –analysis approach tested & tailored to objectives
- –towards markers valid / reproducible /applicable for purpose

Methodological research required