MRC | Biostatistics Unit

KING'S College LONDON

NHS National Institute for Health Research

Designing a preliminary adaptive study to inform a biomarker trial in Psoriasis

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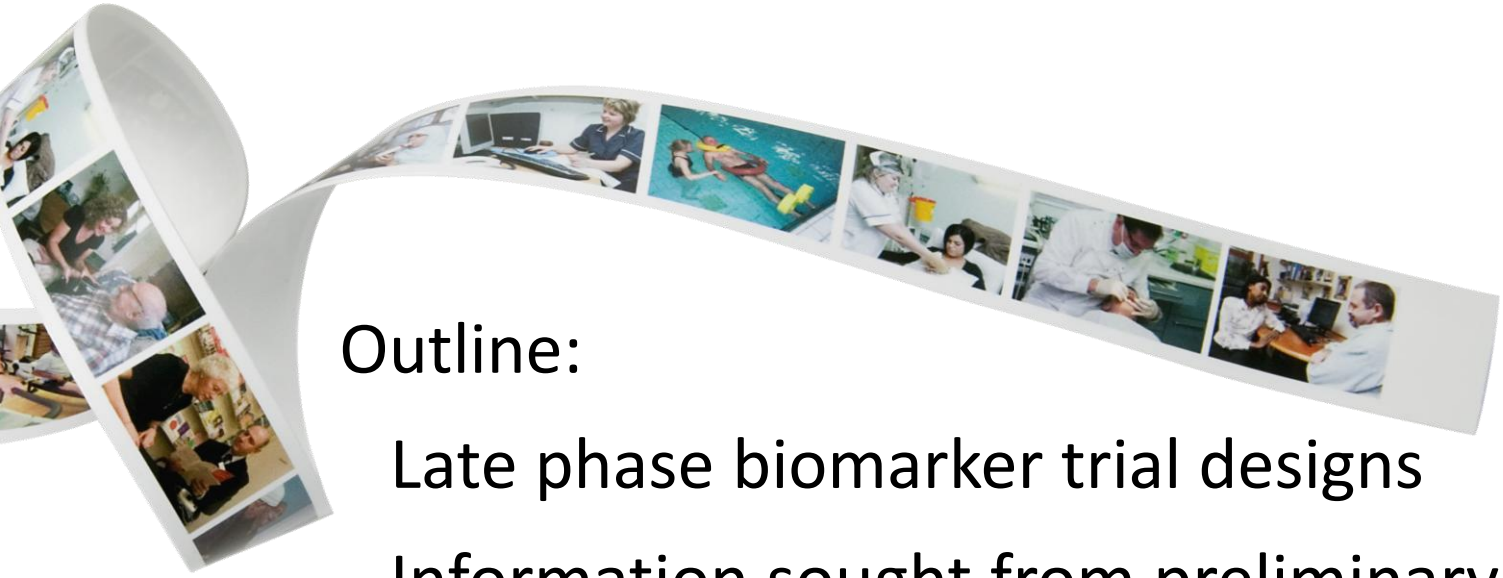
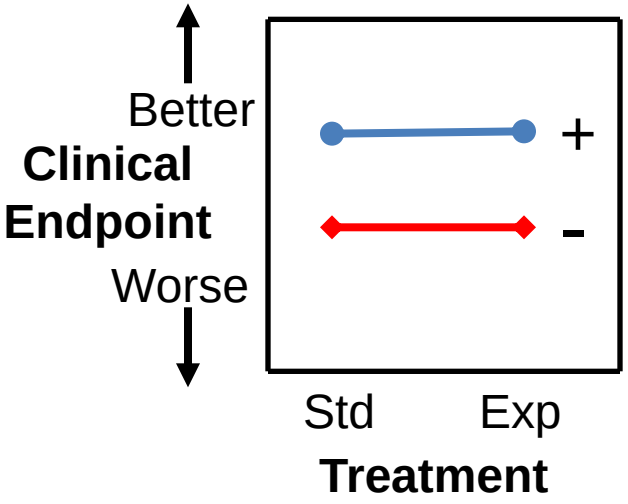


Outline:

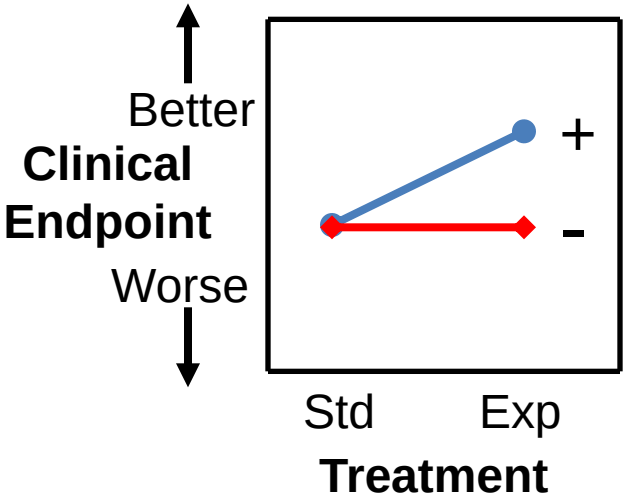
- Late phase biomarker trial designs
- Information sought from preliminary work
- Designing a two-stage study

Biomarkers – classifications and uses



Prognostic:

- associated with **disease outcome**
- risk assess (+,-) to stratify for treatment



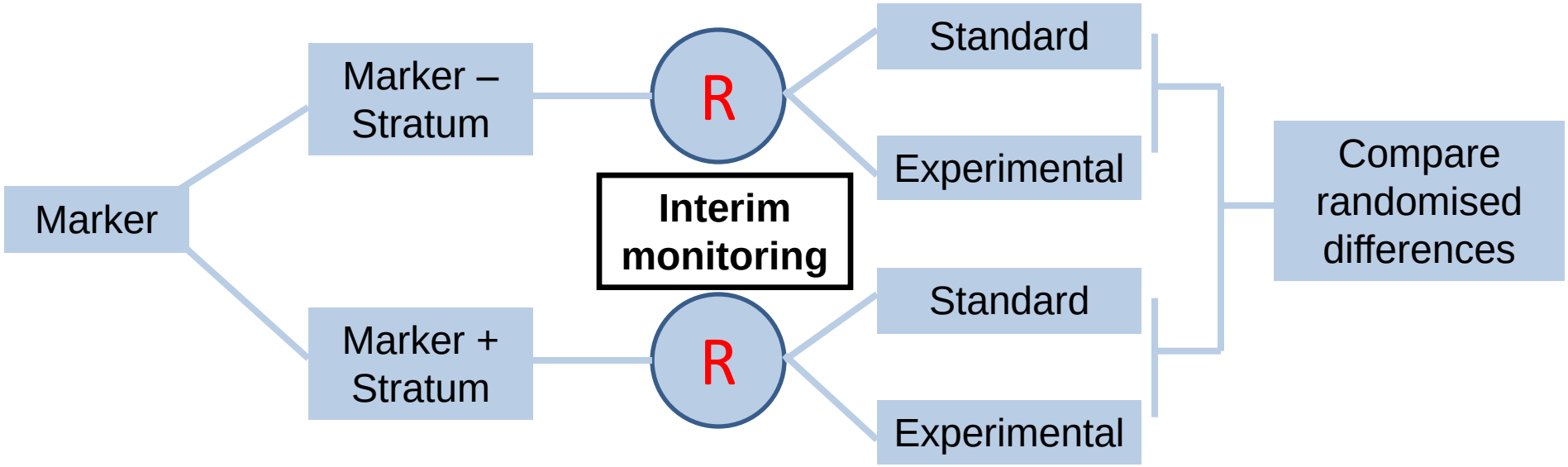
Predictive:

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

Biomarkers – roles in trials of various designs...

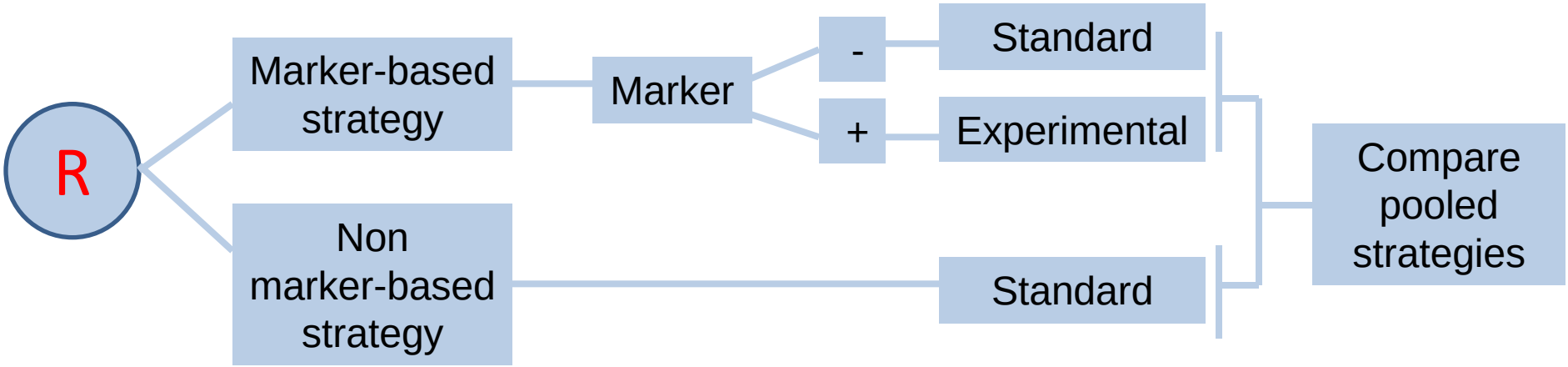
Biomarker-Stratified Design (Full specification)

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



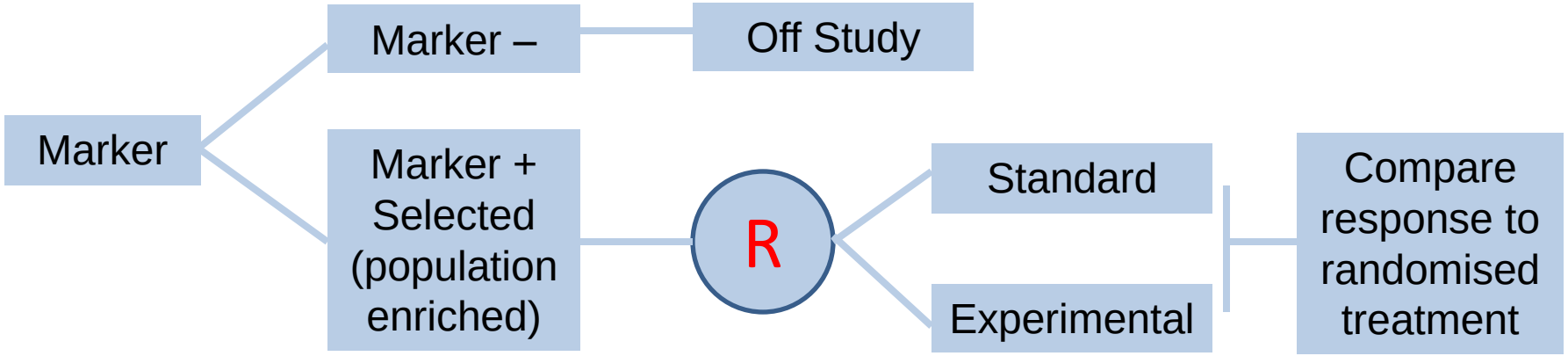
Biomarker-Strategy Design ("Use" vs "Ignore" biomarker)

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

*'Combination of **scientific**, **clinical**, **statistical** and **ethical** considerations'*

Requires early phase studies to fill gaps and increase potential

The “client” and the Psoriasis example

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 score from 17 cytokine profile

But many variables / over-fitted model / abandoned methods
Need to improve **reproducibility** of score → **increased 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)

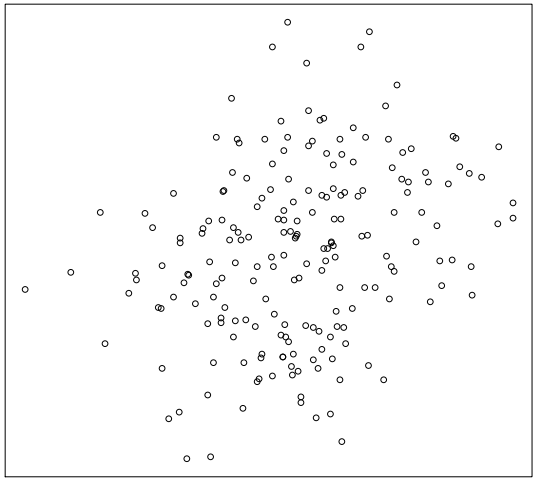
- decline in mean severity score (response)
- decreases in Th17 / Th1 cells (marker)

Assess → patient-level *marker-response* in → **larger** sample
Consider → **control** treatment to establish marker specific to infliximab

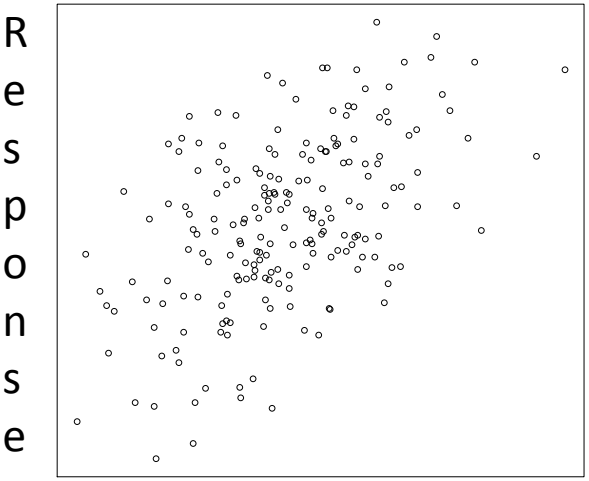
What effect size should be detectable?

(variation in treatment response explained by biomarker)

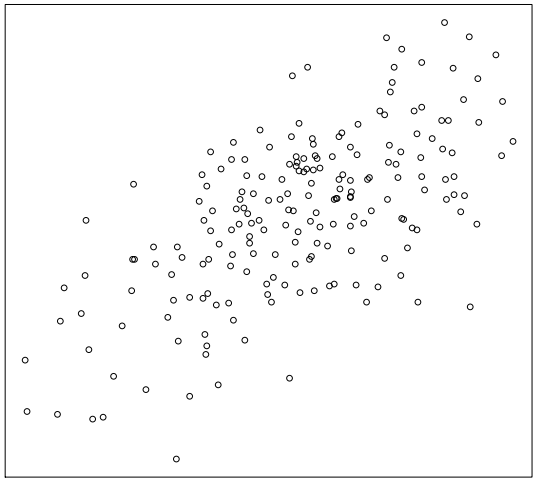
R-squared 10%



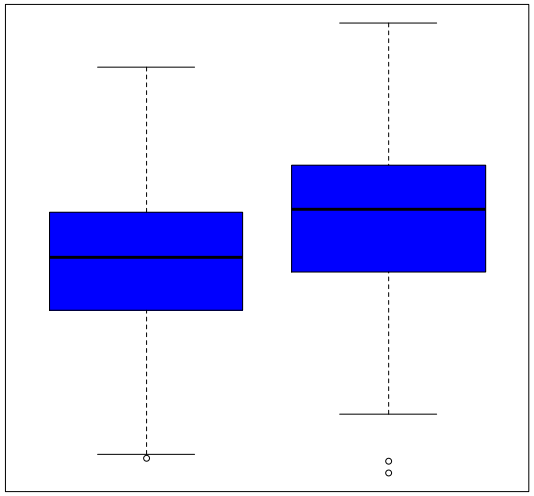
R-squared 20%

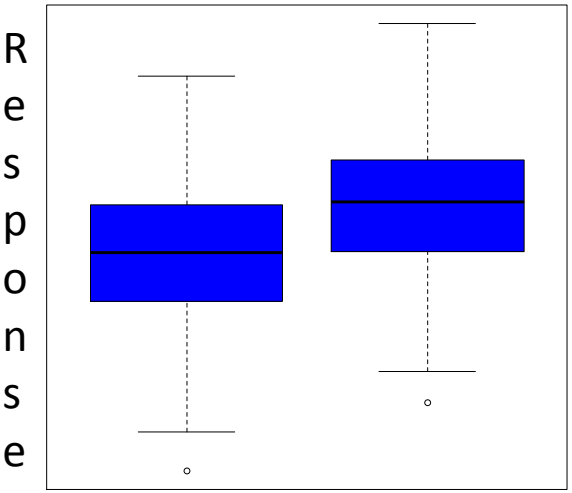


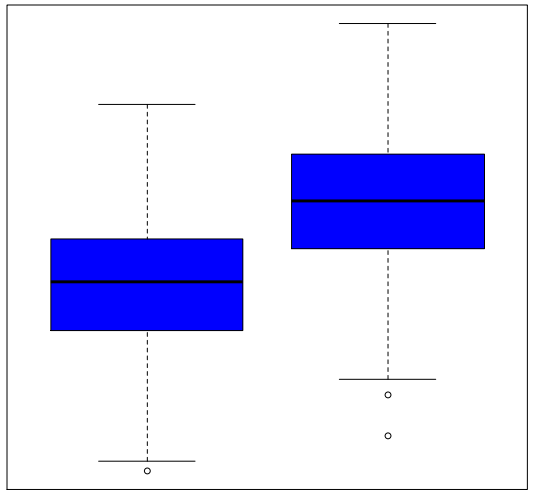
R-squared 40%



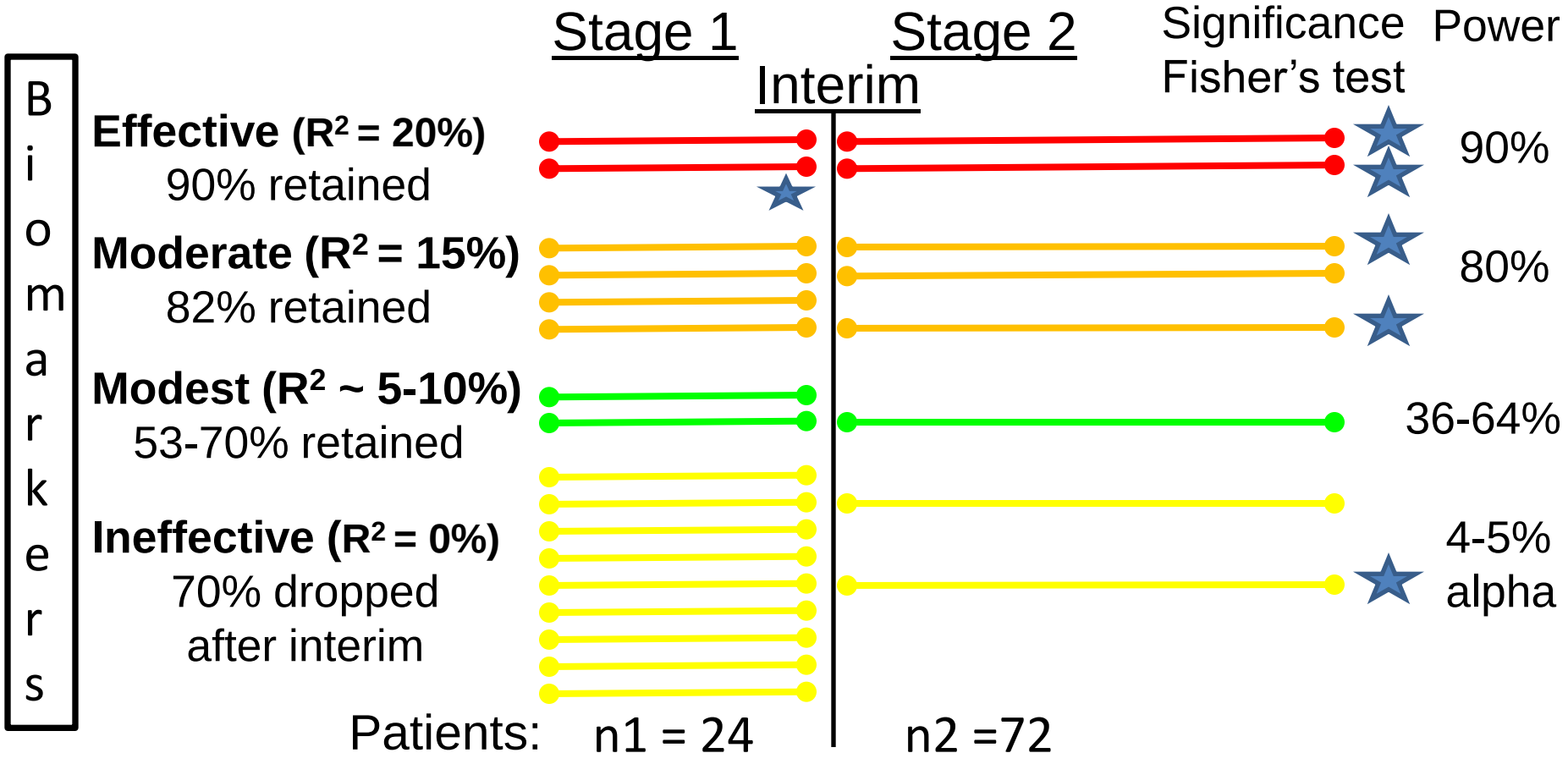
Detect with n=49





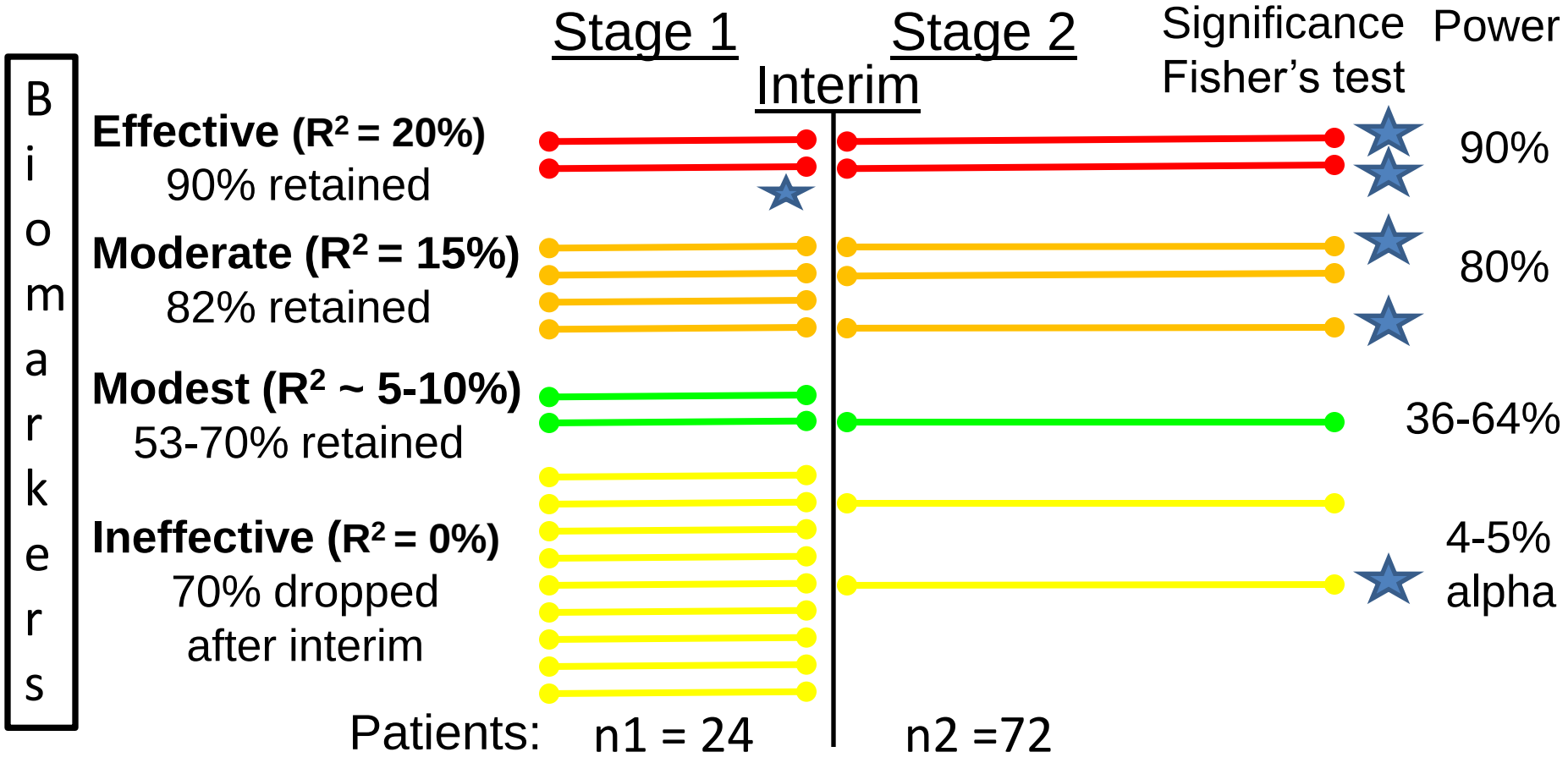


Alternatively: a 2-stage adaptive interim design



- early interim stopping: marker futility ($p > 0.3$; equivalent to $r^2<5\%$)
- additional "guarantee" to retain minimum of 5 best-performers
- 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 little by "the guarantee" (~ 2% and 0.2%)

-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

Conclusions – Biomarker trial design

"One size does not fit all"

Choice of late design depends on information about marker / its role

Early phase studies increase potential

- which biomarkers / treatment specificity
- effect size / combination

Consider adaptive element

- saves on costly markers / larger focus on reduced set

Plan design and analysis together

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

Developments

- Extend unbiased estimation to correlation coefficient

- Compare strategies for developing combinations

- Incorporate biomarker cost

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