A framework for the design and analysis of phase III randomised trials in uncommon diseases

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London Hub

Standard way of designing large trials

Generally accepted by

- funders, regulators, patients, other researchers

Design parameters (type I error, power, targeted effect size,…)

- Lead to large trials
- ‘Doable’ in a reasonable timeframe

What should we do when standard trial design is just too large?

Something has to change in our thinking

Much attention now being paid to very small populations:

- **INSPIRE:** Innovative methodology for small populations research
- **IDEAL:** Integrated design & analysis of small population group trials
- **ASTERIX:** Advances in small trials design for regulatory innovation and excellence

and more…

How can we change our thinking?

- Sacrifice concurrent control?
- Sacrifice randomisation?
- Switch to a Bayesian inferential framework?

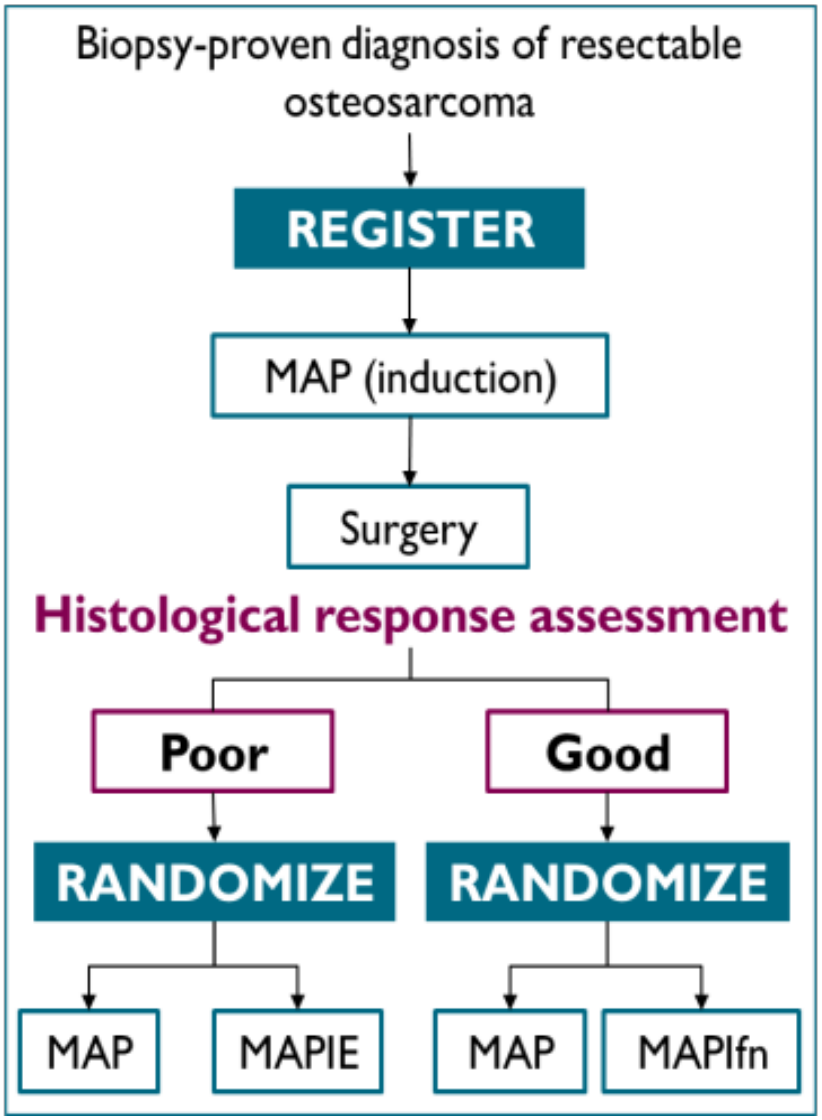
Unfamiliar to funders, regulators, patients and other researchers

How do they compare quality of evidence to a more traditional design?

→ **Reduced acceptance?**

What to do between the extremes?

EURAMOS-1: Bone Tumours



Rare disease

US : <1 case / 1,500 people

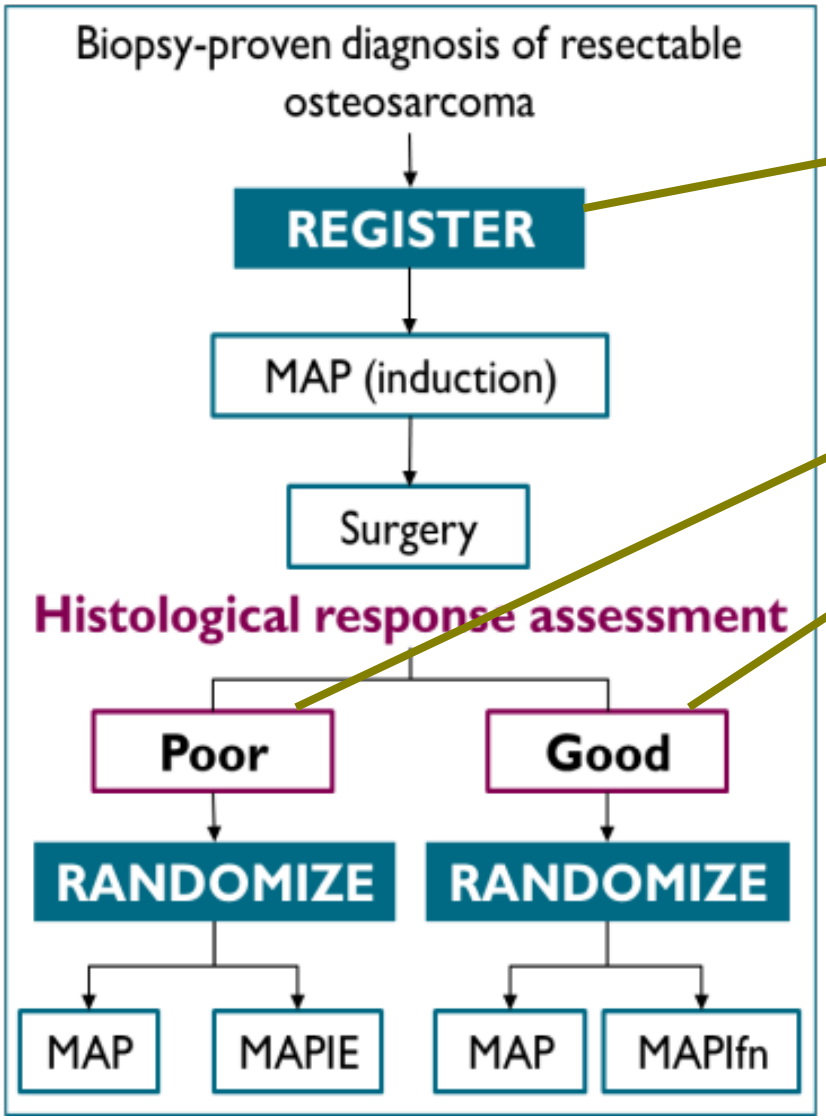
EU : <1 case / 2,000 people

Japan: <1 case / 2,500 people

Osteosarcoma = 200 cases/yr UK

1 case / 300,000 people

EURAMOS-1



Accrual targets

1,400 patients registered

693 poor responders

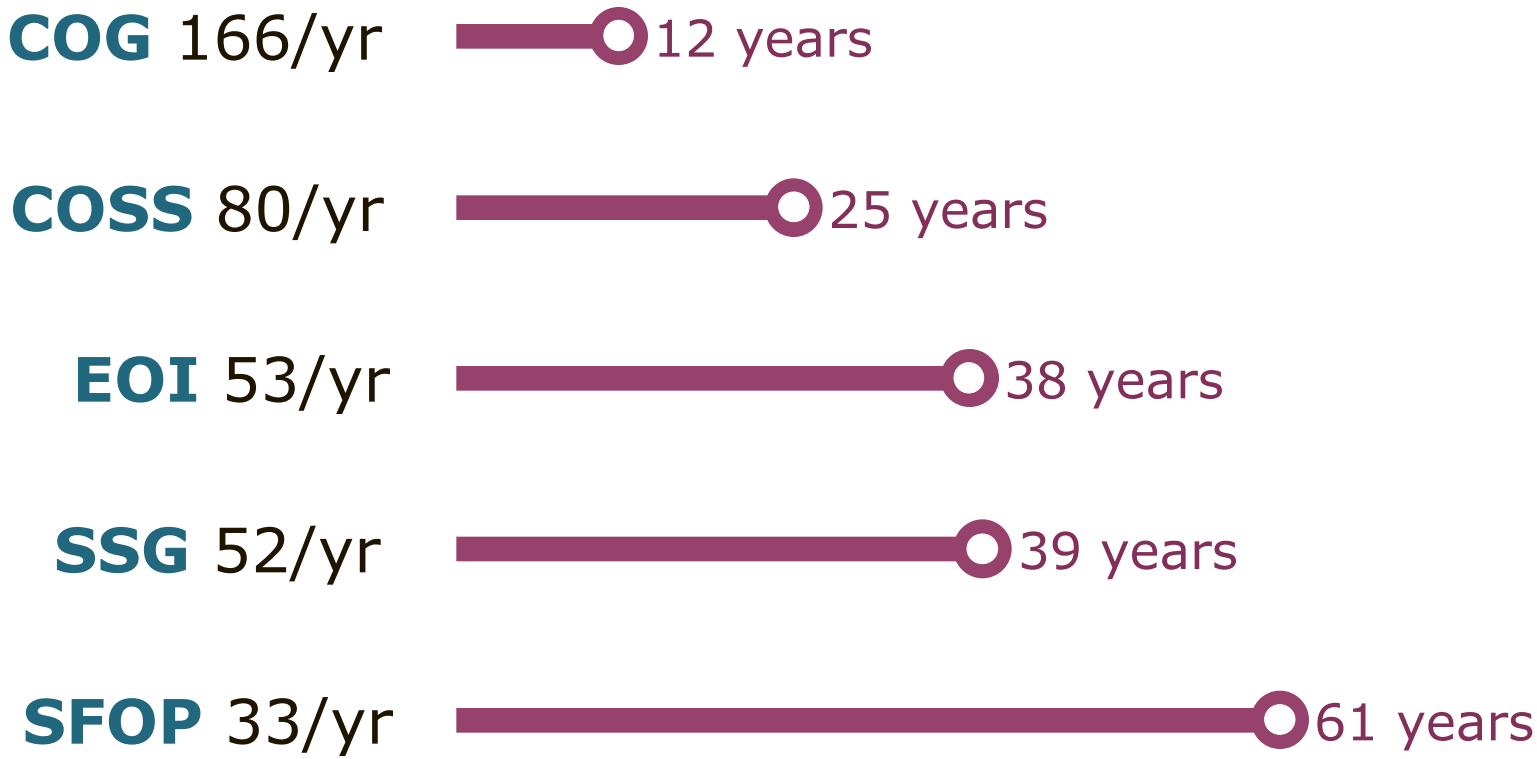
567 good responders

1,400 revised to 2,000 during recruitment

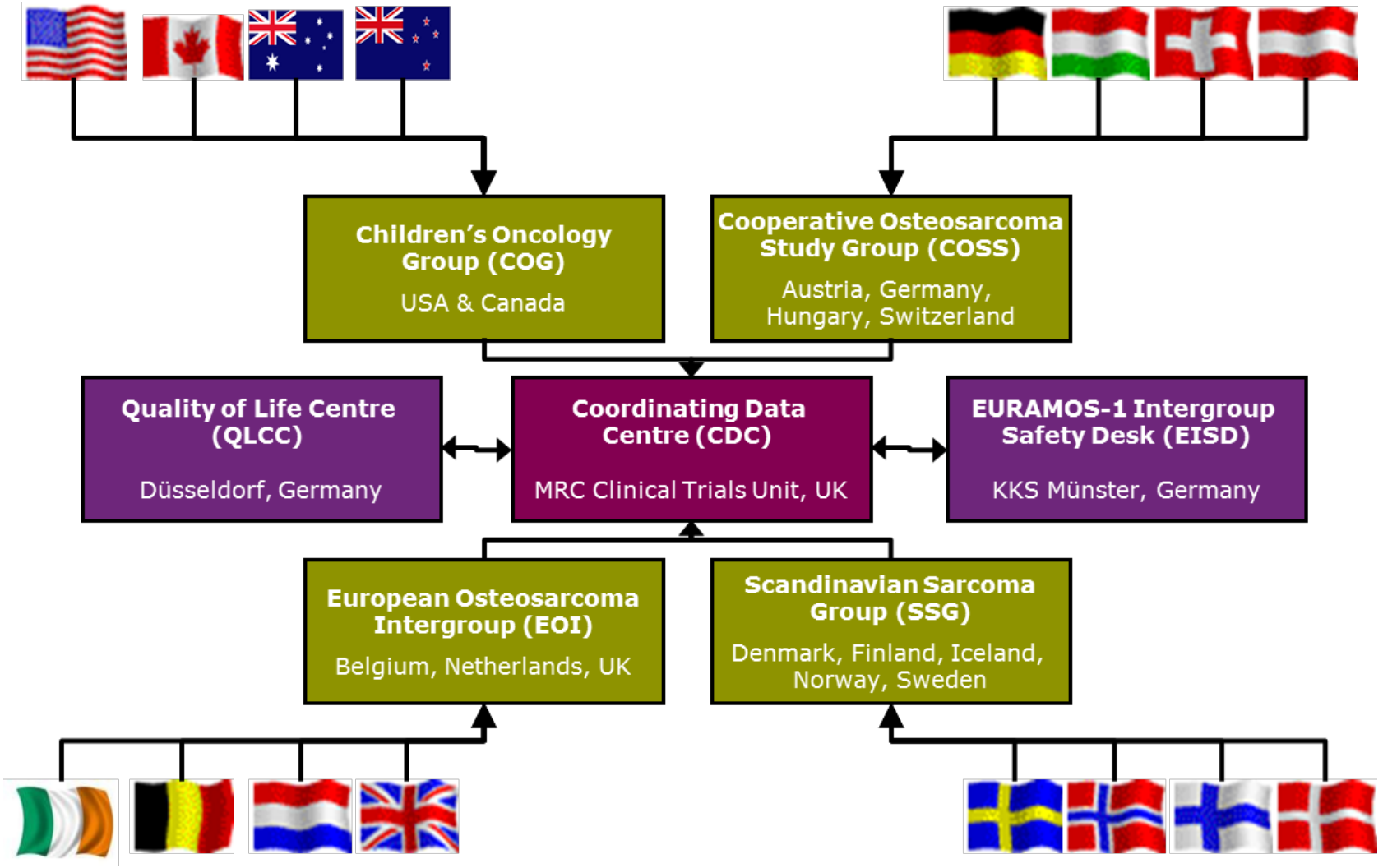
– no regional group can achieve this

Osteosarcoma groups

Time to 2,000 patients



EURAMOS-1 collaboration



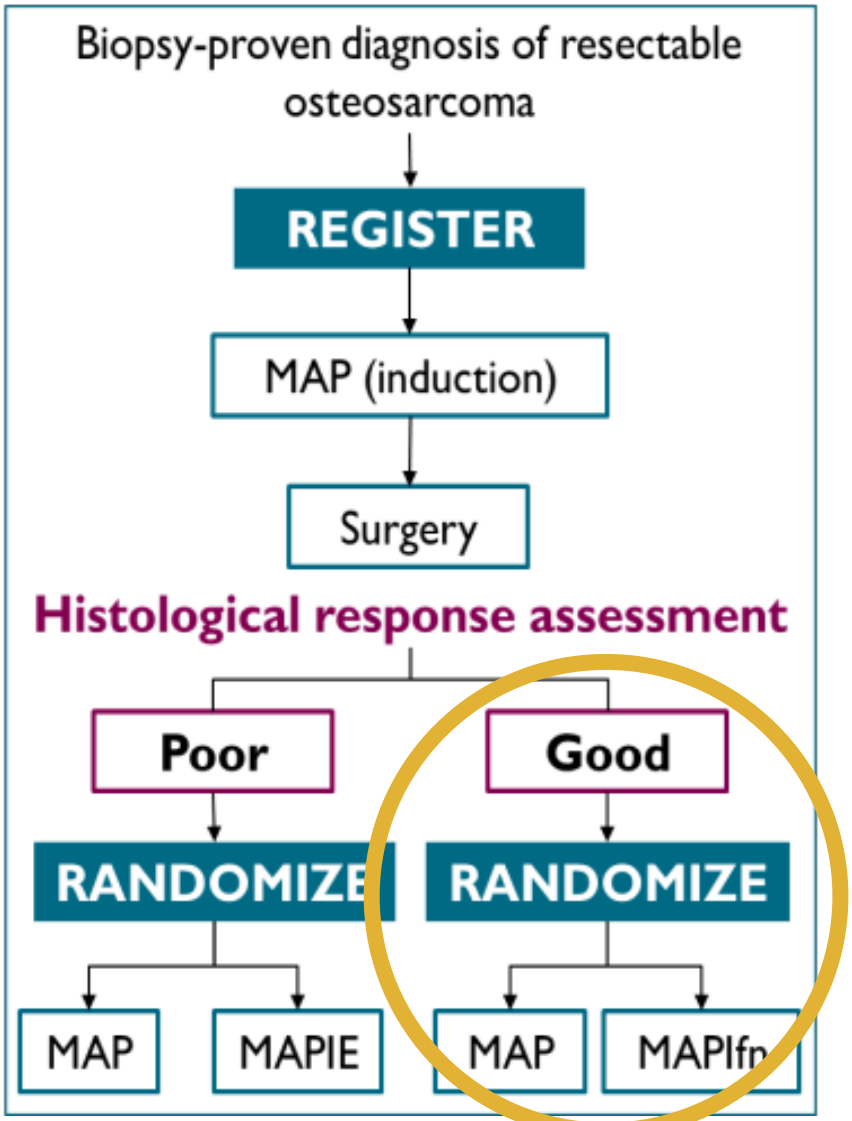
EURAMOS-1

EURAMOS-1 was our best shot at improving treatments for osteosarcoma in 10 years

- Too many patients to switch to designs for really rare diseases
- Too few patients to do a ‘regularly’ designed trial

How could we have designed it differently to maximise randomised information on treatment effect with the numbers we could recruit?

EURAMOS-1 good responders



Primary OM	**Event-free survival**
Ctrl. Events	**70% event-free at 3yr**
Target	**HR=0.63 → 10% abs diff**
Power	**80%**
Alpha	**5%, two-sided**
Events	**147**
Patients	**567**

Framework:
Information-heavy outcomes

- We know we should aim to maximise the information content of the data

Continuous > **time-to-event** > **categorical** > **binary**

- Time-to-event information is defined by no. events. If clinically relevant,

Progression-/disease-free survival > **overall survival**

Framework
Sample size: Power

Context:

- Limited number of trials
- Few chances of improving treatments
- Don’t want to miss something worthwhile

‘Arbitrary’ use of 80 or 90% power in most trials

Framework proposal: **Don’t** compromise on power

Framework
Sample size: Target difference

Best source?

- Other diseases
- History

Some trials target larger difference. However:

- No reason to think treatment effect is larger
- Will miss relevant differences due to low power for realistic difference

Framework proposal: **Do not** compromise (too much) on target difference

Framework
Sample size: Type I error

- Conventions for power and significance levels have come from pragmatic choices
- Scientific parameters determined by what is feasible
- We propose the making these pragmatic choices when patient numbers are more limited

Framework
Sample size: Type I error

5% generally chosen

Can accept larger Type I error rate

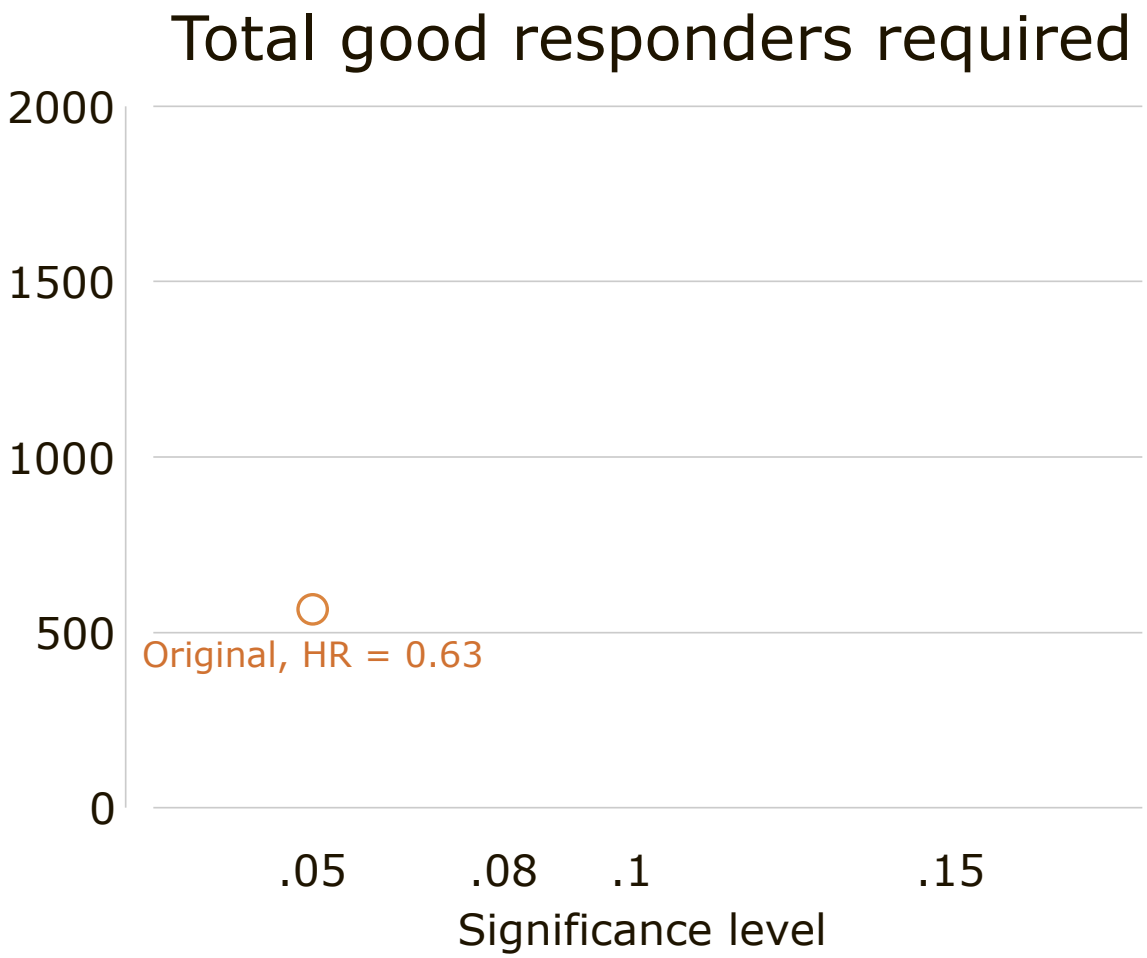
- Very few trials in this 'uncommon disease'
- Many more trials in more 'common diseases'

Are two-sided tests necessary in *superiority* trials?

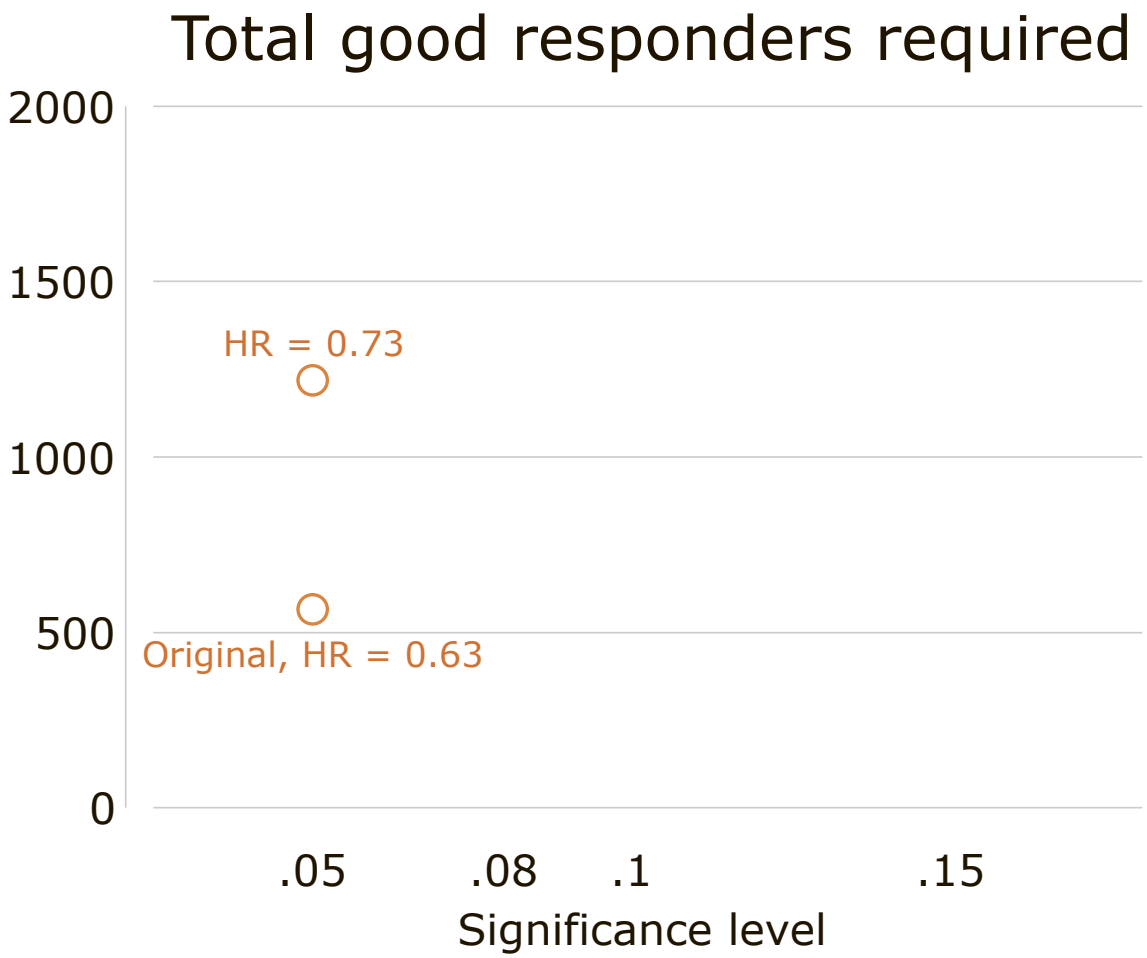
- They are not called *any-difference* trials'!

Framework proposal: **Compromise** on alpha and move to 1-sided tests

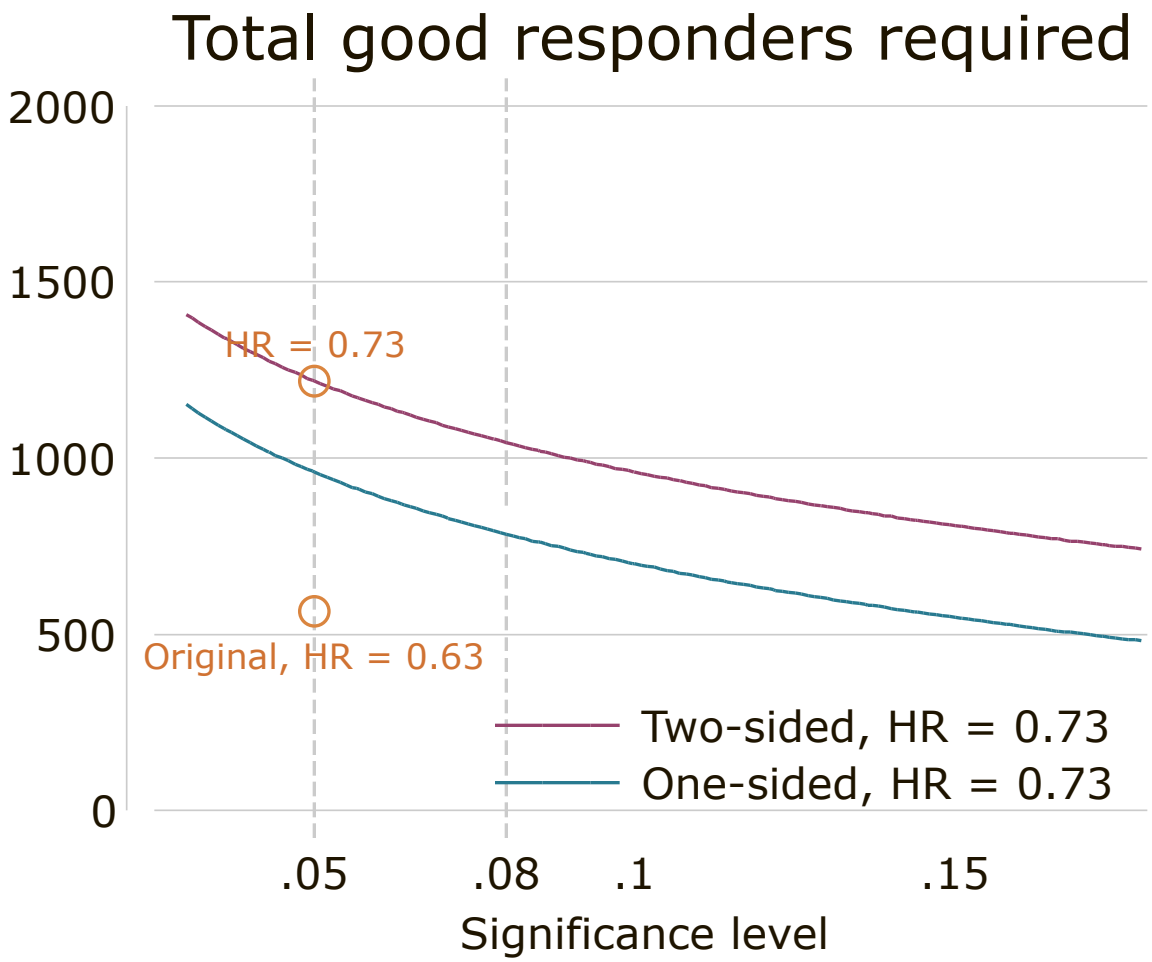
Framework
Sample size: Type I error



Framework
Sample size: Type I error



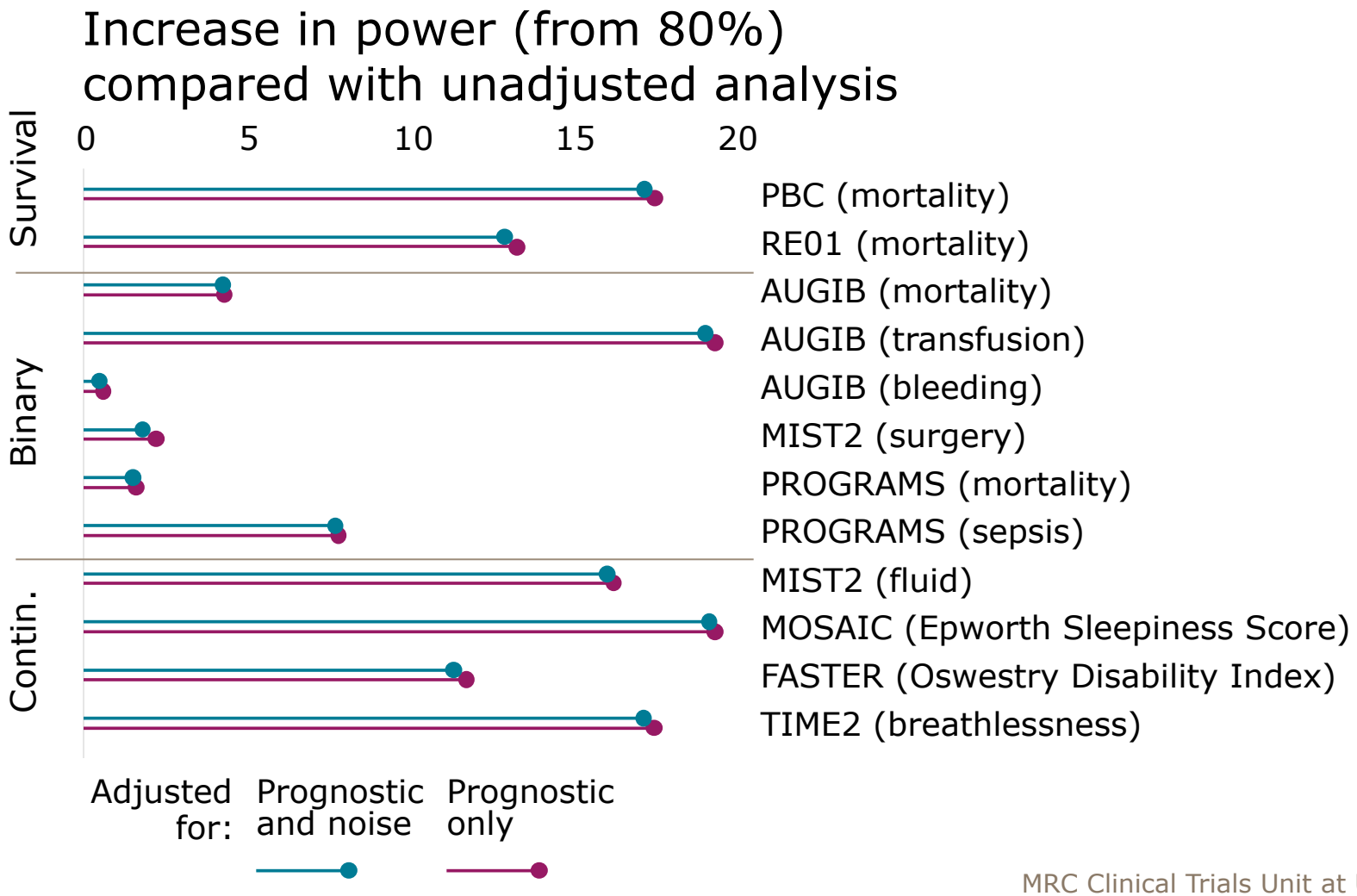
Framework
Sample size: Type I error



With a realistic HR, sample size rockets

We can bring this some way back down by relaxing significance level and using one sided tests

Framework
Including covariates

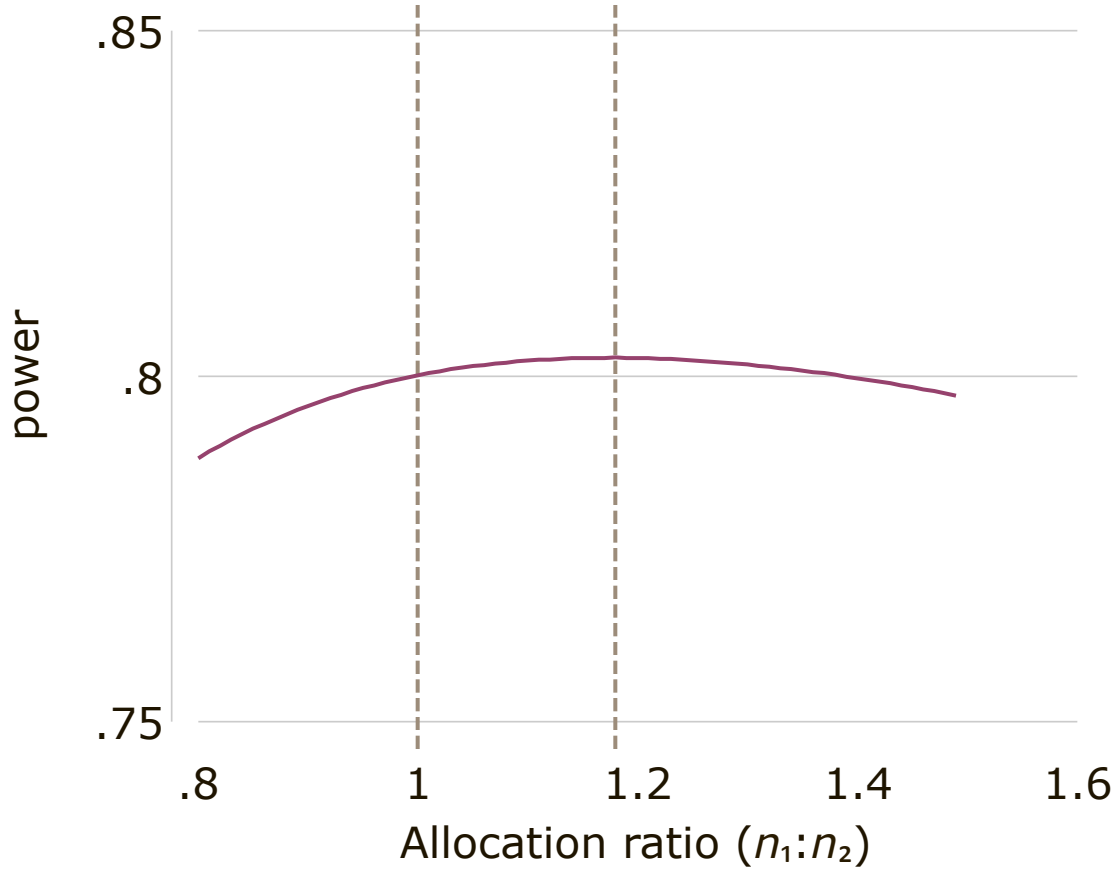


Framework
Including covariates

- Can improve power more than you might expect
- With many covariates and few patients/events, covariate *adjustment* can be tricky
- An attractive recent alternative is to weight on the inverse estimated propensity score (E Williamson, Statist. Med. 2014)

Framework proposal: **Include covariates** you suspect to be prognostic

Framework:
Skewing allocation



Can improve power, but hardly worth the effort

This isn't a reason *not* to skew: if you have another good reason, may lead to slight gain or loss in power

Framework:
Re-randomisation

Can be used when certain conditions are fulfilled:

1. Patients continue to be eligible
2. Patients complete follow up for previous treatment period before being re-randomised
3. Assumption of constant treatment effect across all randomisation periods is reasonable
4. Randomisation must be unrestricted within patient – random whether they switch or stick

Kahan BC, Forbes AB, Doré CJ, Morris TP.

A re-randomisation design for clinical trials.

BMC Medical Research Methodology 2015; **15**(1), 96.

Framework proposal: **Include covariates** you suspect to be prognostic

Framework:
Other aspects

Selection of research treatment

- Do not compare Tweedledum vs. Tweedledee
- Maximise the difference between research and control

Need to carefully think through consequences making a type I error

Using external information

- Particularly important for adverse events?
- Might be important to justify relaxed type I error

Framework applied to EURAMOS-1

Proposals	**EURAMOS-1 re-design**
→ Use info-heavy OMs	**X** EFS already best OM
→ Compromise on alpha	√
→ One-sided tests	√
→ Non-traditional values	√
→ Consider covariates at design	? via simulation?
→ Skew allocation ratios	√ Skew allocation ratios
→ Re-randomise patients	**X** Wouldn't be eligible – progressive condition

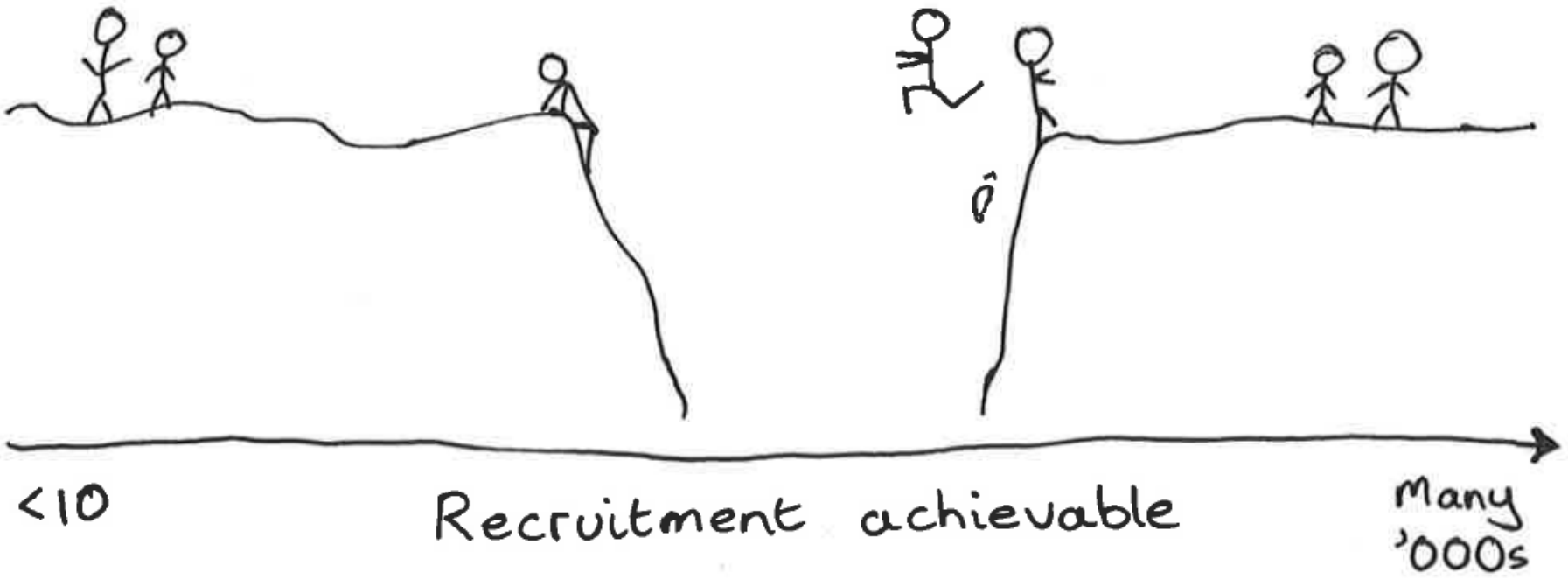
Framework applied to EURAMOS-1

	Original	**Revised #1**
Primary OM	Event-free survival	Event-free survival
Ctrl Events	70% event-free at 3yr	70% event-free at 3yr
Target	HR=0.63 → 10% abs diff	HR=0.73 → 8%
Power	**80%**	**80%**
Alpha	**5%, two-sided**	**15%, one-sided**
Allocation	**1C : 1R**	**4(C) : 5**
Events	**147**	**210**
Patients	**567**	**928**

Framework applied to EURAMOS-1

	Original	**Revised #2**
Primary OM	Event-free survival	Event-free survival
Ctrl Events	70% event-free at 3yr	70% event-free at 3yr
Target	HR=0.63 → 10% abs diff	HR=0.73 → 8%
Power	**80%**	**80%**
Alpha	**5%, two-sided**	**8%, one-sided**
Allocation	**1C : 1R**	**1 : 1**
Events	**147**	**276**
Patients	**567**	**1,208**

What to do between the extremes?



What to do between the extremes?

- Need to bridge the gulf
- ‘All we can do is use the information at hand to make the best decision possible’

  – Wedding Crashers
- ‘A way to do more trials, not a way to do small trials when larger ones are possible’

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MRC Hubs for Trials Methodology Research
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Framework
Sample size: **Type I error**

A thought experiment:

Assume you know nothing about the ritual of using 80 or 90% power and 5% (rather 2.5%) significance.

You are asked to provide acceptable risks of claiming

1. A good treatment doesn't work
2. A useless treatment works

Would you answer (1) **10**% and (2) **2.5**%?

Have you used these in practice?

Framework
Sample size: **Type I error**

No scientific worker has a fixed level of significance at which, from year to year, and in all circumstances, he rejects hypotheses; he rather gives his mind to each particular case in the light of his evidence and his ideas.

– RA Fisher (1956)

1. People do exactly that
2. Scientific workers are not always male

EURAMOS-1 collaboration