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## Introduction and Motivation

Recently, several models predictive of the placebo response have been published for pain RCTs. Predictive placebo models could be used to:

- support enrichment strategy,
- conduct adjusted statistical analysis (e.g. with covariate).

We have investigated the benefit/cost ratio of both approaches using real and simulated clinical study data.

## Study Designs and Patients

This clinical trial was a randomized, double-blind, placebo-controlled, single-dose, parallel-group study to assess the efficacy, safety, and tolerability of a single-dose IA administration of a new drug in 180 patients with moderate to severe painful knee OA.

## Placebo Model

A predictive placebo model [Branders et al., OARSI 2021] was prospectively applied to all patients of the study.

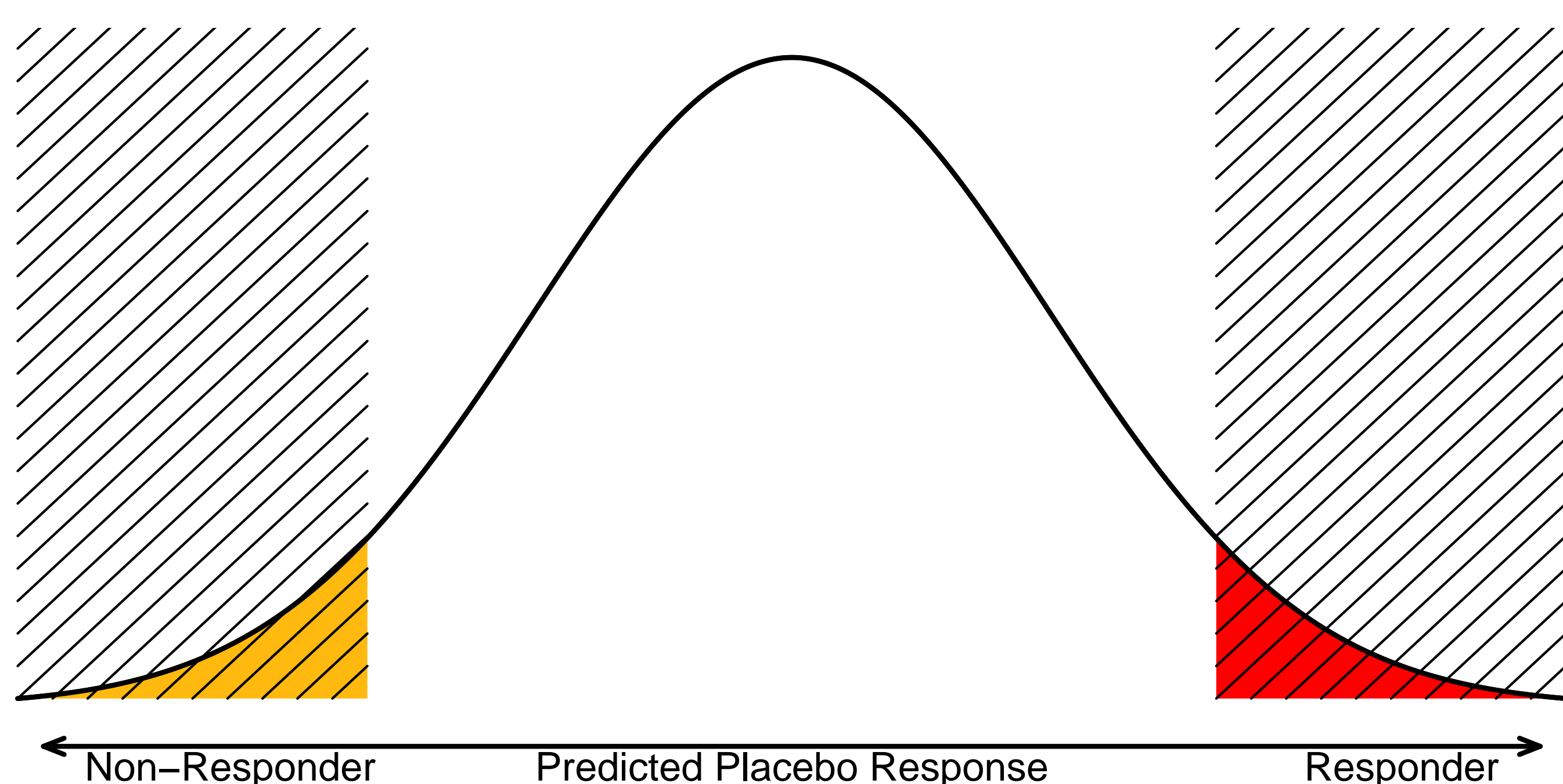
The model calculated the expected placebo response of patients at baseline using patients' baseline characteristics (traits of personality, demographics, history and severity of disease).

The model was able to explain 35.6% ( $p < 0.001$ ) of the placebo variance and 27.7% of the total variance of the primary endpoint (WOMAC-Pain).

## Enrichment Strategy

The expected benefit of excluding and replacing extreme patients, such as strong placebo responders, before the randomization in an enrichment procedure is to increase the assay sensitivity.

**Figure 1:** Patients predicted to be strong placebo responders or non-responders by the model were excluded.



This enriched screening strategy was evaluated by the gain in treatment effect precision while excluding up to 30% of the patients.

Assuming a normal distribution, the gain in treatment effect precision with the enrichment is:

$$Precision\_Gain = \frac{1}{1 - R^2(1 - \sigma_{trunc}^2)} \quad (1)$$

Where  $R^2$  is the variance explained by the model,  $\sigma_{trunc}^2$  is the variance of a truncated  $N(0, 1)$  distribution.

## Covariate Adjustment

The placebo model predictions are used as covariate in the estimation of the treatment effect as any covariate (like age, gender, etc).

The gain in precision with the covariate adjustment is easy to compute:

$$Precision\_Gain = \frac{1}{1 - R^2} \quad (2)$$

Where  $R^2$  is the variance explained by the model.

In theory, the adjustment will always have better precision gain than the enrichment.

## Simulation Results

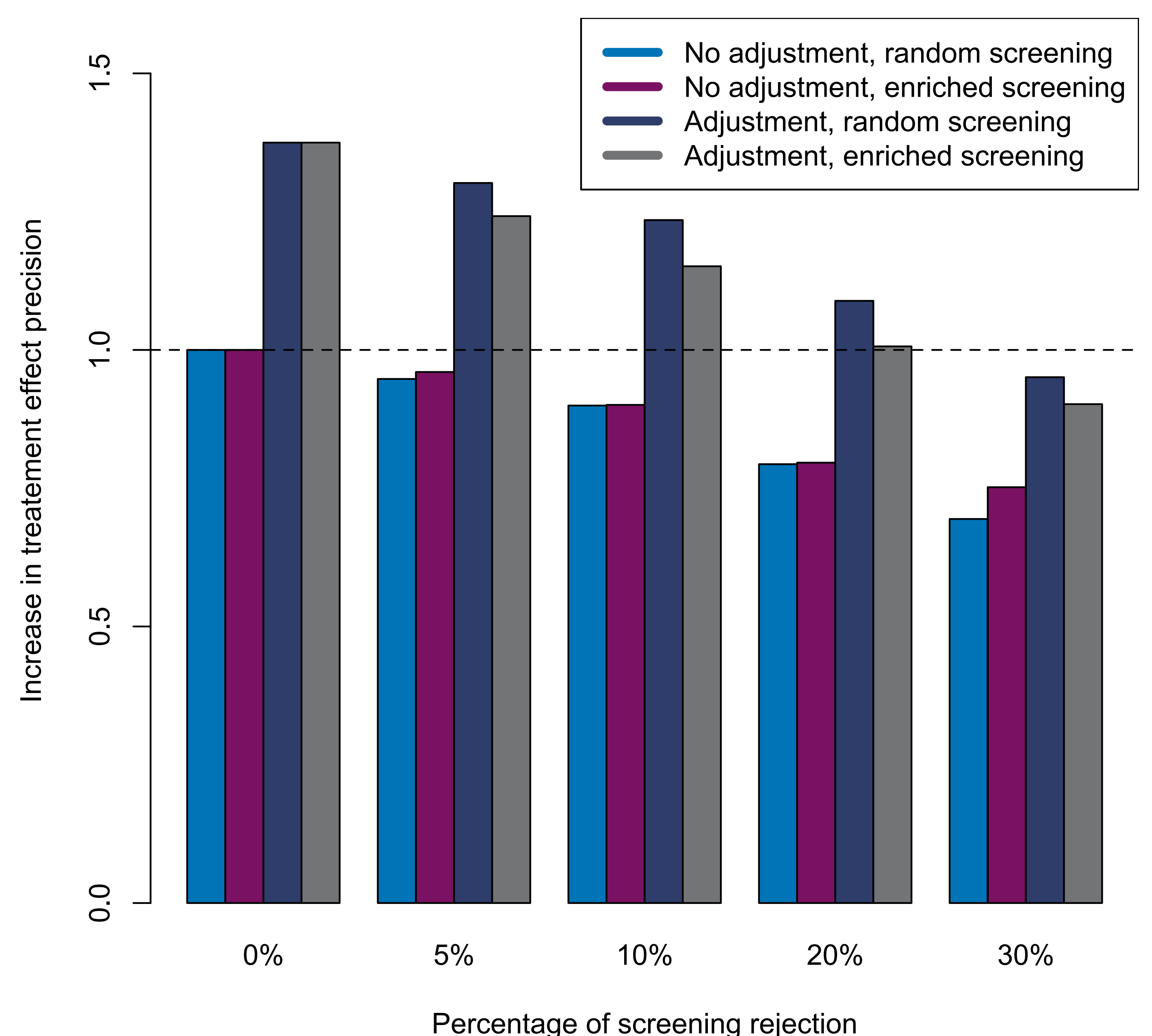
In the simulations, the enrichment strategy can improve the precision at the cost of a large number of patients excluded and replaced.

However, even doubling the number of screened patients to optimize the enrichment strategy yields only 80% of the gain of an adjusted analysis.

## Treatment response precision

To simulate the replacement of the excluded patients during the enrichment, we compare the approach with a random screening procedure excluding the same percentage of patients from the study.

**Figure 2:** The precision of the four procedures (enriched screening or not, with and without covariate adjustment) was compared to the precision of non-adjusted analysis with 0% of patients excluded.



For all procedures (■, ■, ■, and ■), the increased exclusion of patients was associated with a decrease in precision.

For the random screening procedures (■, ■), this decrease is proportional to the number of patients excluded.

Without adjustment, the enriched screening procedure ■ has only a marginal gain in precision as compared to random screening ■. When removing 30% of the patients, the precision increases only from 0.69 without enrichment ■ to 0.75 with the enriched screening ■.

The covariate adjustment alone ■ increased the treatment effect precision by +37% for the random screening approach ■.

Covariate adjustment ■ is superior to the enrichment without adjustment ■.

Combining enriched screening and adjustment ■ does not improve further the precision of the treatment effect estimation ■.

## Conclusions

Enrichment screening strategies are simple and appealing. However, covariates adjusted analyses have better theoretical gains.

We estimated the real impact on the assay sensitivity of such strategies in phase II study with moderate to severe painful knee OA patients.

Our work demonstrates the limited benefit of excluding placebo responders compared to adjustment of the analyses for the predicted placebo response.

Covariate adjustment can lead to significant gains in precision and power.