

# Using short-term evidence to predict 6-month outcomes in clinical trials of signs and symptoms in rheumatoid arthritis

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## Background

### What is rheumatoid arthritis?

- A chronic, systemic inflammatory disorder that principally attacks the joints producing an inflammatory synovitis that often progresses to destruction of the articular cartilage.

### What is an ACR20 and ACR50 response?

- Composite binary measures of response of a patient to RA treatment. Essentially, ACR (American college of rheumatology) 20 and ACR50 correspond to a 20% and a 50% improvement over a period of time.

### What do we want to know?

- We have a new biologic treatment for RA. We want to predict the ACR response after 6 months of treatment.

### What data do we have?

- Data from a **1-month clinical trial**. This gives the number of patients who have an ACR response after treatment with the new biologic drug for 1 month.
- Summary data from the literature** on other biologic drugs. This gives the number of patients who have an ACR response at 1 and 6 months.

## Objective

- To develop a model to predict the probability of an ACR20 and ACR50 response **after 6 months** for a new biologic drug for rheumatoid arthritis, when **1-month** ACR20 and ACR50 response data are available.

## Data from the literature

### What were the inclusion and exclusion criteria?

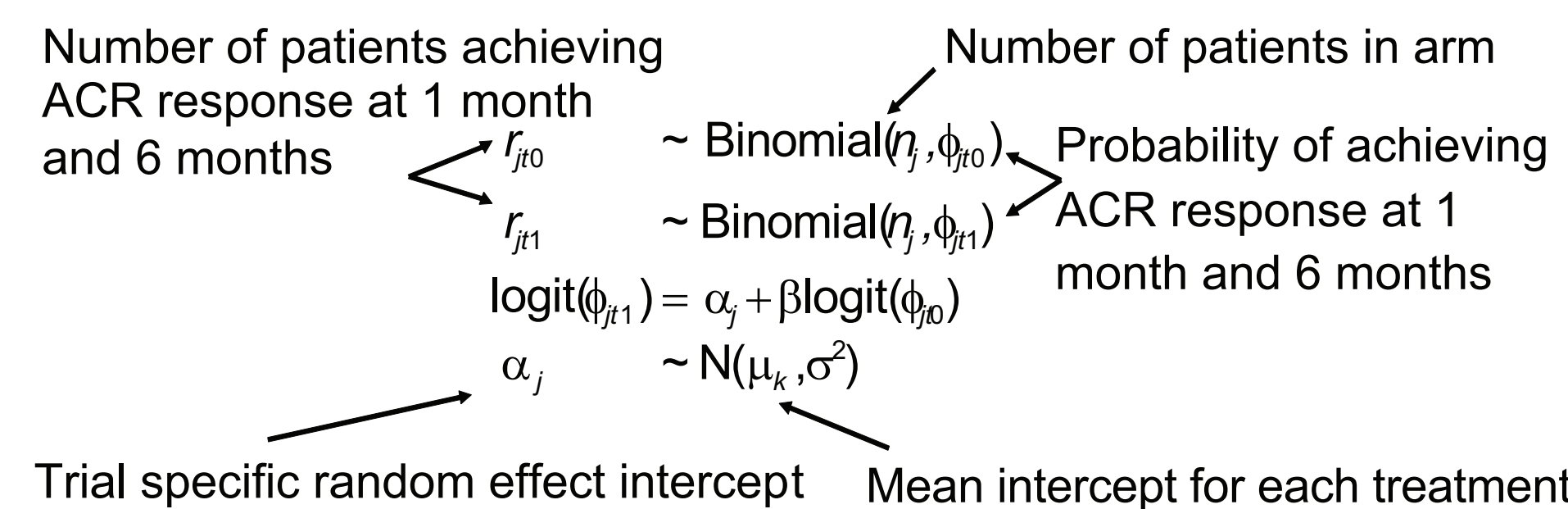
- Randomized controlled trials of biologic agents compared to placebo or methotrexate (MTX).
- At least 6 months duration.
- ACR20 or ACR50 at 1 and 6 months are reported.
- Published between 1 Jan 1980 and 1 Jan 2005.

### What studies were found?

- 11 trials were included in the analysis. Of the 11 trials, 3 studied anakinra, 4 studied etanercept, 1 studied infliximab, and 3 studied adalimumab.
- There was information from 37 different active treatment arms: 8 MTX, 12 biologic monotherapy, and 17 biologic plus MTX.
- 29 provided data for 1 month and 6 months for ACR20; 24 provided data for 1 month and 6 months for ACR50.

## Model

- 'j' denotes the treatment arm within each trial and 'k' denotes the treatment type used (1=MTX; 2=biologic monotherapy; 3=biologic plus MTX).



## Main model assumptions

- The probability of response at 6 months depends upon the probability of response at 1 month through a logistic regression.
- The logistic regression has a slope parameter, that is independent of the study arms, and an intercept parameter that is dependent upon the particular study arm.
- Intercept parameter is a normally distributed random effect, with a different random effect mean for each type of treatment.
- This acknowledges the existence of heterogeneity between trial arms. We are assuming that each treatment arm is exchangeable with any other, even across the clinical trials themselves.

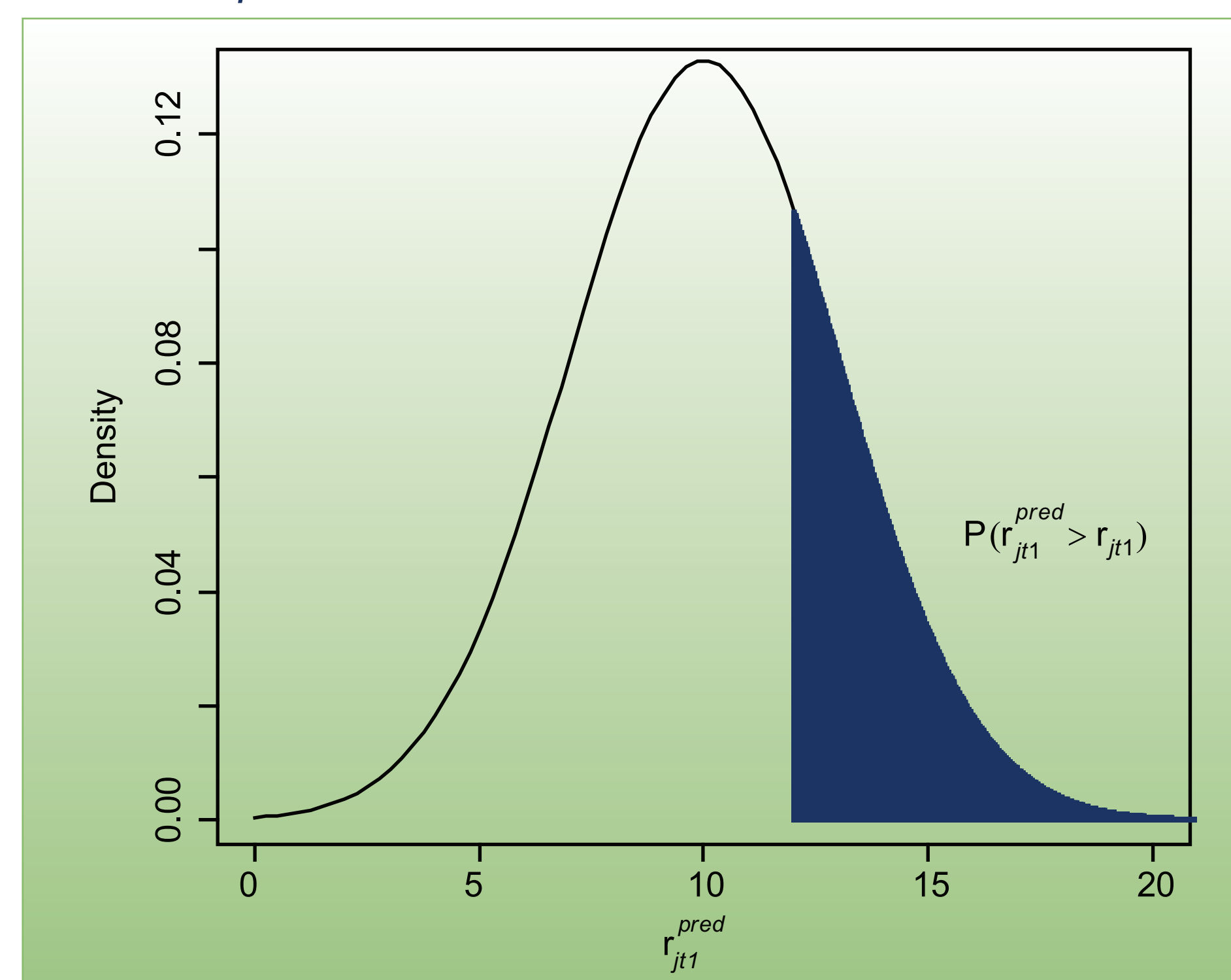
## Model checking – Bayesian predictive P-values

### What are Bayesian predictive P-values?

- One sided tail probabilities that the data predicted by the model are more extreme compared to the observed data.
- This is a goodness-of-fit approach to assess the validity of a model.
- $r_{jt1}$  is observed response rate at 6 months for each data point j.
- $r_{jt1}^{\text{pred}}$  is the response rate predicted by the model (Figure 1).

$$\text{Predictive } P\text{-value} = P(r_{jt1}^{\text{pred}} \geq r_{jt1} | r_{jt1})$$

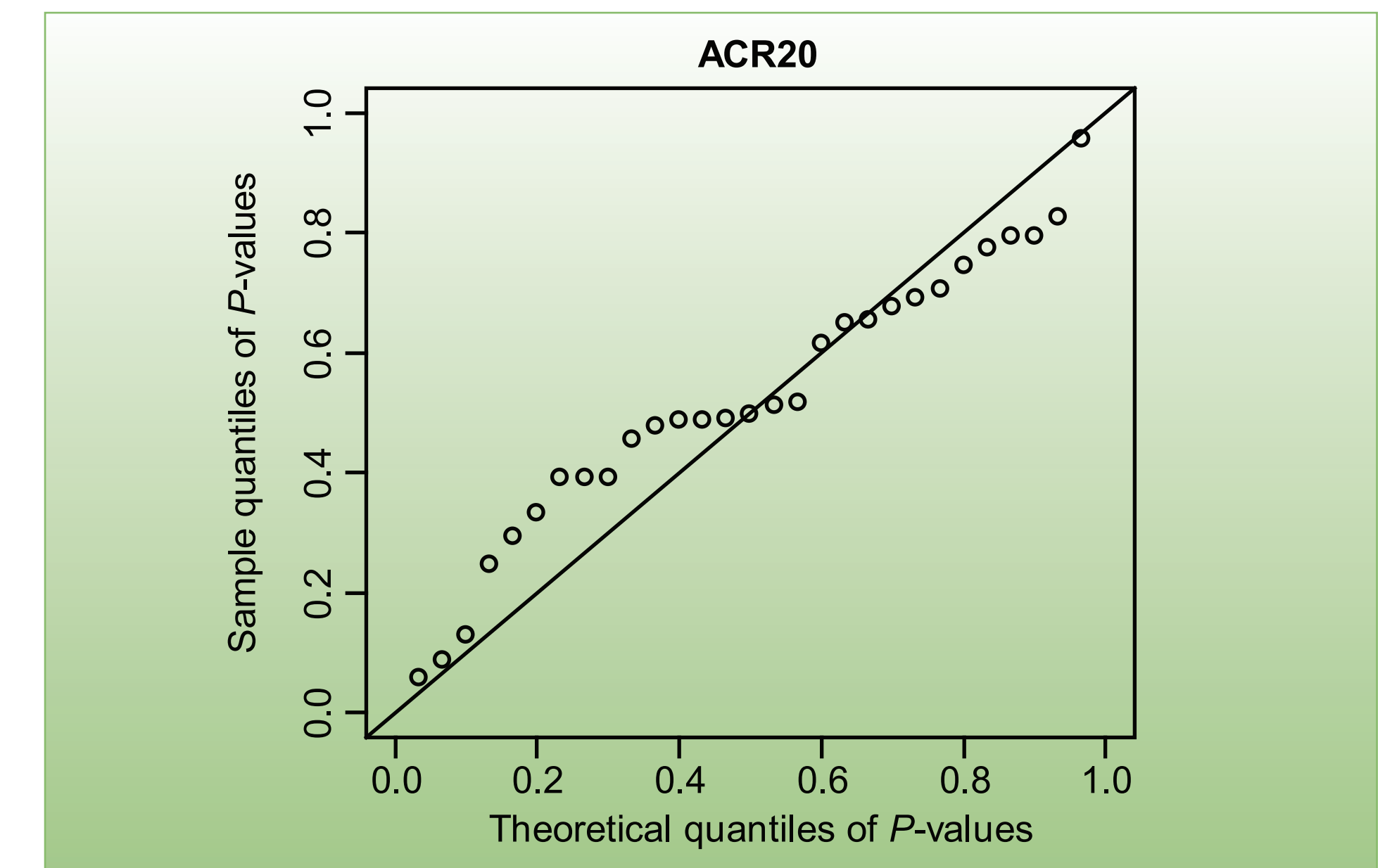
Figure 1: Distribution for a predicted data point. Shaded area shows the predictive P-value



### How do you use Bayesian predictive P-values?

- If the predictive distribution from the model represents the data well the predictive P-values will have a uniform distribution between 0 and 1.
- Test this by plotting the sample quantiles of the predictive P-values against the quantiles of a standard uniform distribution. The points should lie on a straight line (Figure 2).

Figure 2: Plot of the quantiles of the predictive P-values against the theoretical quantiles assuming the model is correct



## Using the model for prediction

- Suppose a clinical trial for the new drug has 30 patients and 15 of them have an ACR20 response at 1 month.  $n_{\text{new}} = 30$  and  $r_{\text{new}, t0} = 15$ .
- Find the probability of a response at 6 months  $\phi_{\text{new}, t1}$ .
- (1) Estimate the probability of response at 1 month  $r_{\text{new}, t0}$ .
- (2) Estimate the study random effect intercept  $\alpha_{\text{new}}$ .
- (3) Estimate the probability of response at 6 months  $\phi_{\text{new}, t1}$ .

$$\begin{aligned} r_{\text{new}, t0} &\sim \text{Binomial}(n_{\text{new}}, \phi_{\text{new}, t0}) \\ \alpha_{\text{new}} &\sim N(\mu_3, \sigma^2) \\ \text{logit}(\phi_{\text{new}, t1}) &= \alpha_{\text{new}} + \beta \text{logit}(\phi_{\text{new}, t0}) \\ &= \text{logit}'(\phi_{\text{new}, t1}) \end{aligned}$$

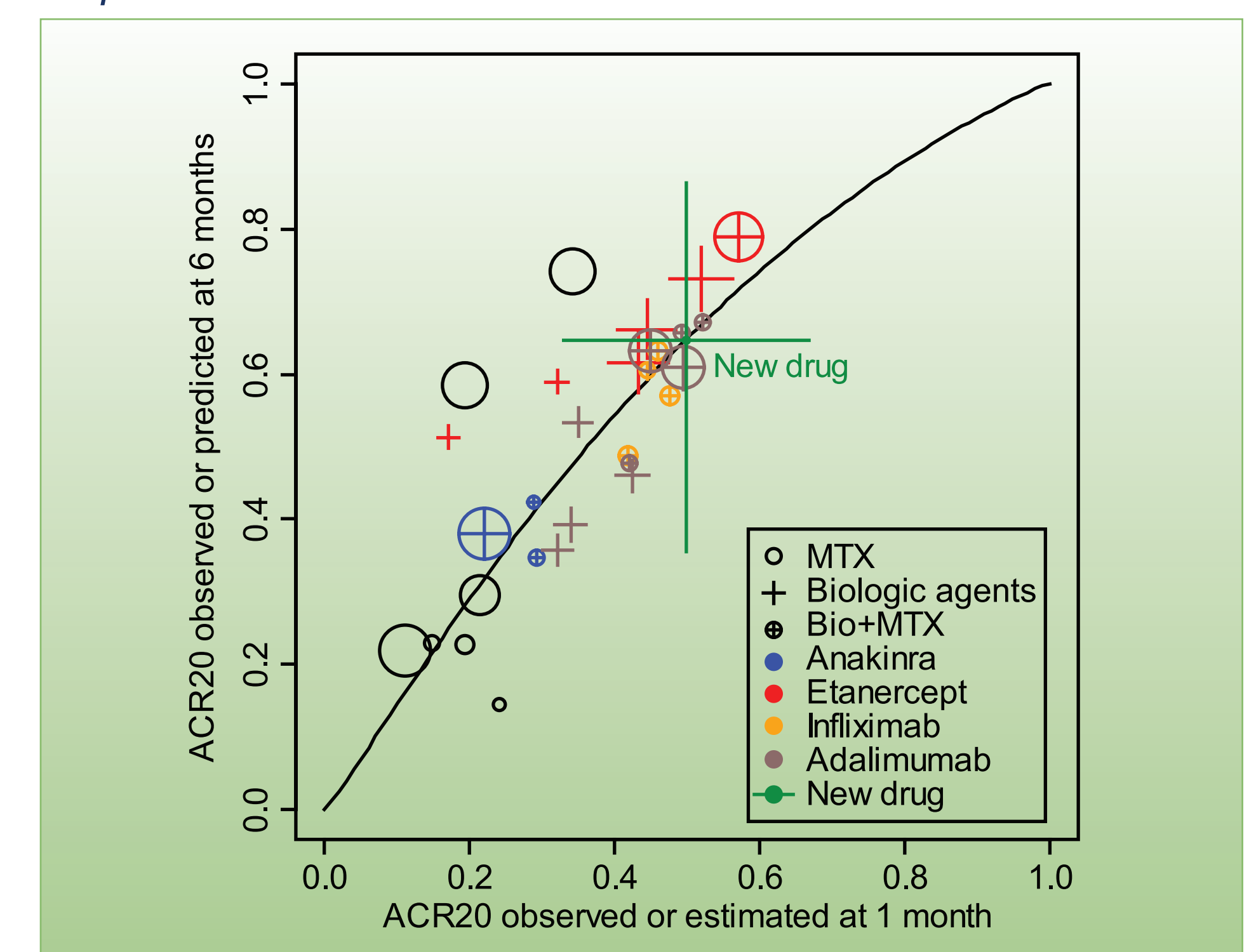
### For the literature data from existing biologics

- Plot the observed ACR response at 1 and 6 months.

### For the new drug

- Plot estimated ACR response at 1 month and predicted response at 6 months.
- The horizontal green line shows the uncertainty in the estimated response at 1 month.
- The vertical green line shows the uncertainty in the predicted response at 6 months (Figure 3).
- Uncertainty in the predicted response includes uncertainty in ACR measured in the trial and uncertainty in the prediction model.

Figure 3: Plot of the observed or estimated ACR20 responses at 1 and 6 months



## References

- Nixon RM et al. Pharm Stat. 2008 Oct 23. [Epub ahead of print]. DOI. Available at <http://dx.doi.org/10.1002/pst.351>.