Assessing the Safety of Rosiglitazone for the Treatment of Type II Diabetes

A Bayesian Approach

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Joint work with: Kostas Kalogeropoulos and Larry Phillips

How to assess a drug?

Subject ID	Treatment Group	Nausea	Dyspesia	Haemoglobin
233	1	1	1	-3.2
342	2	0	1	-4.7
213	1	1	0	1.4

Figure 1: Sample clinical trial dataset. Decisions about drugs are based on summaries of datasets like this.

How to Assess a Drug?

Regulatory Timeline:

1999 Rosiglitazone gets US approval

2000 Rosiglitazone gets European approval

2007 New evidence for risks arises [Nissen and Wolski, 2007]

2010 European regulators revert their recommendation

2011 US regulators partially revert their recommendation

2013 US regulators undo reversion

How to Assess a Drug?

Average Treatment Effects

Treatment Group	Nausea	Dyspesia	Hemoglobin
1	12%	8%	-0.5
2	13%	10%	-4.1

How to Assess a Drug? A General Framework

1. Clinical trials data are recorded in a matrix Y
2. Characterize the distribution of effects
3. Need to combine effects into a single value s, termed *preference score**
4. $P(s^T > s^C|Y)$, generalize from the trial to the population

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Multi-criteria Decision Analysis, in a single slide

1. "Standardize" each measured variable to a common scale
   $[\text{worst measurement}, \ldots, \text{best measurement}] \rightarrow [0, \ldots, 100]$
2. Choose appropriate weights w_j for each effect
3. Construct the weighted sum $S = \sum_j w_j \cdot c_j$, called *preference score*
4. Compare the *preference scores* s^C and s^T for the control and treatment groups, respectively

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Issues/Goals

[Phillips et al., 2013] proposed using MCDA for drug assessment.

Issues:

- assumes independence of effects (correlation of mixed data)
- individual variability

Goals:

- Calculate $P(s^T_{N+1} > s^C_{N+1}|y)$ taking into account
- address above issues

Model

For binary data:

$$\begin{cases} Y_{ij} \sim \text{Bernoulli}(\eta_j),\ i = 1, \ldots, N,\ Y_{ij} \text{ independent, for fixed } j \\ h_j(\eta_j) = \mu_j + Z_{ij}, \end{cases} \tag{1}$$

For continuous variables:

$$Y_{ij} = \mu_j + Z_{ij},\ i = 1, \ldots, N. \tag{2}$$

where the distribution of Z is assumed to be

$$Z_{i:} \sim \mathcal{N}_J(0_J, \Sigma), \tag{3}$$

$Z_{i:}$ are independent $\forall i$

Model Objectives

The aim is to sample from

$$\pi(\mu, \Sigma, Z|Y) \propto f(Y|Z, \mu, \Sigma)\pi(Z|\Sigma)\pi(\mu)\pi(\Sigma) \tag{4}$$

(for control and treatment groups) so that we can in turn sample from the score posterior.

We can then

1. compute $P(s^T > s^C|y)$ as before
2. compute $P(s^T_{N+1} > s^C_{N+1}|y)$ for a future individual $N+1$ based on

$$\pi(Z_{N+1}|y) = \int\int \pi(Z_{N+1:}|\mu, \Sigma)\pi(\mu, \Sigma|y)\, d\mu\, d\Sigma$$

3. compute $P(s^T_{N+1} > s^C_{N+1}|y, \widehat{\mu}, \widehat{\Sigma})$ based on Bayes or ML estimators of $\widehat{\mu}$,$\widehat{\Sigma}$.

How to Assess Rosiglitazone?

Using a clinical trial dataset

- 150 subjects in Control
- 152 subjects in Treatment (Rosiglitazone)

Testing for 6 effects:

- diarrhea (8.9)
- nausea (17.8)
- dyspepsia (1.8)
- edema (0.5)
- hemoglobin levels (59.2)
- glucose levels (11.8)

MCMC Samples

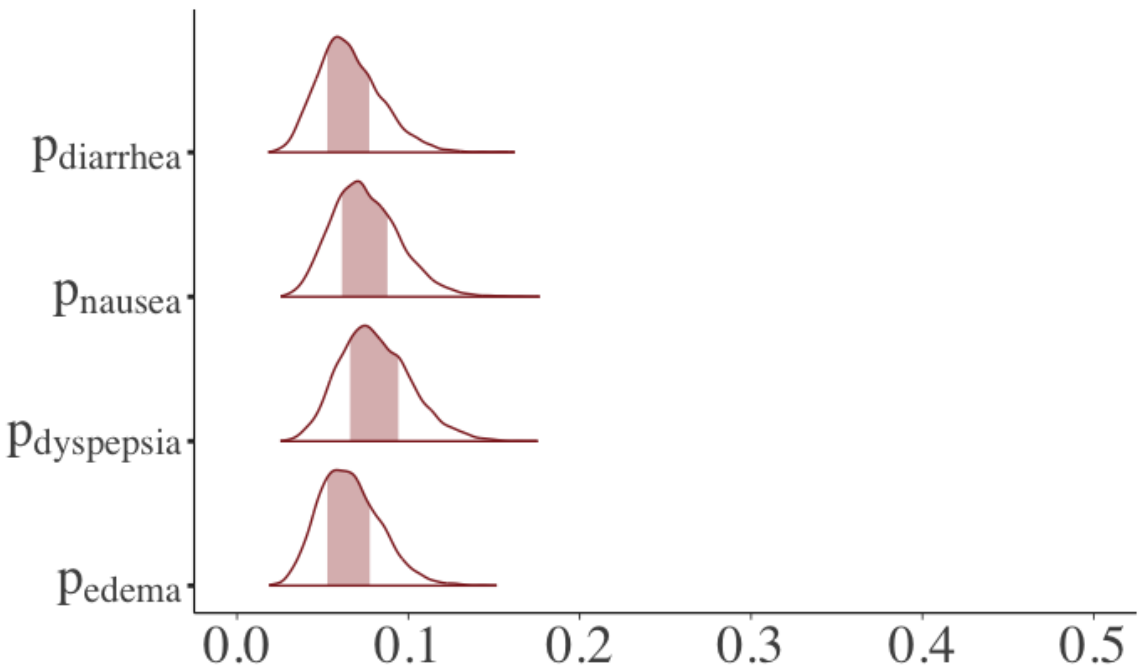


Figure 2: Probability of experiencing an effects for 4 binary effects.

MCMC Samples

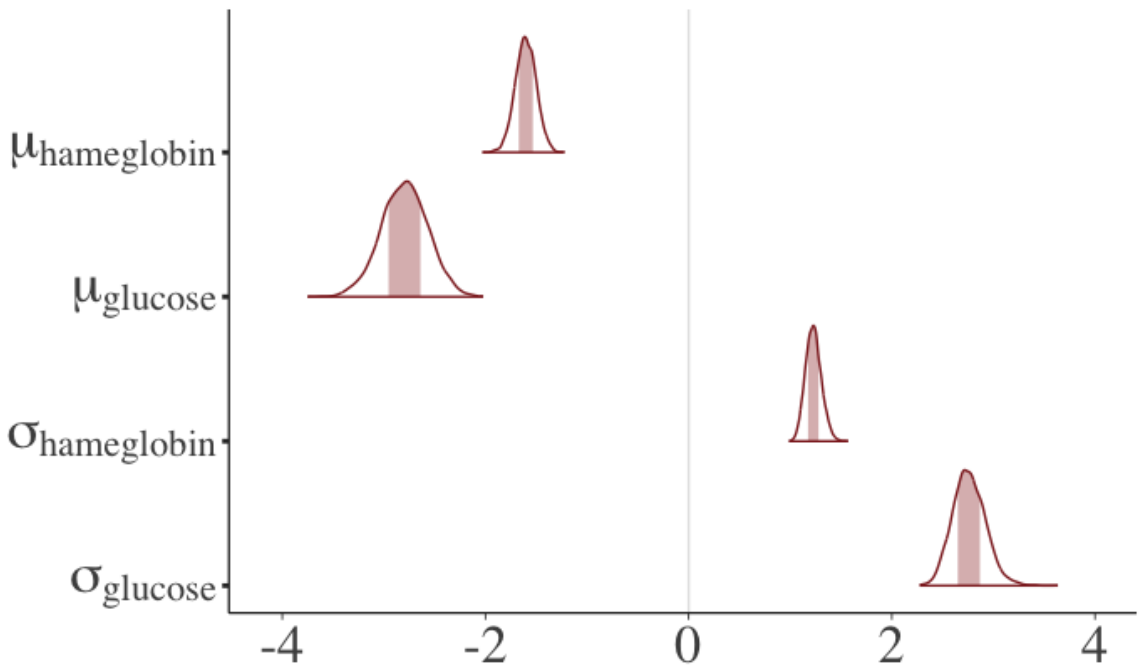


Figure 3: Mean and standard deviations for the 2 continuous effects.

MCMC Samples

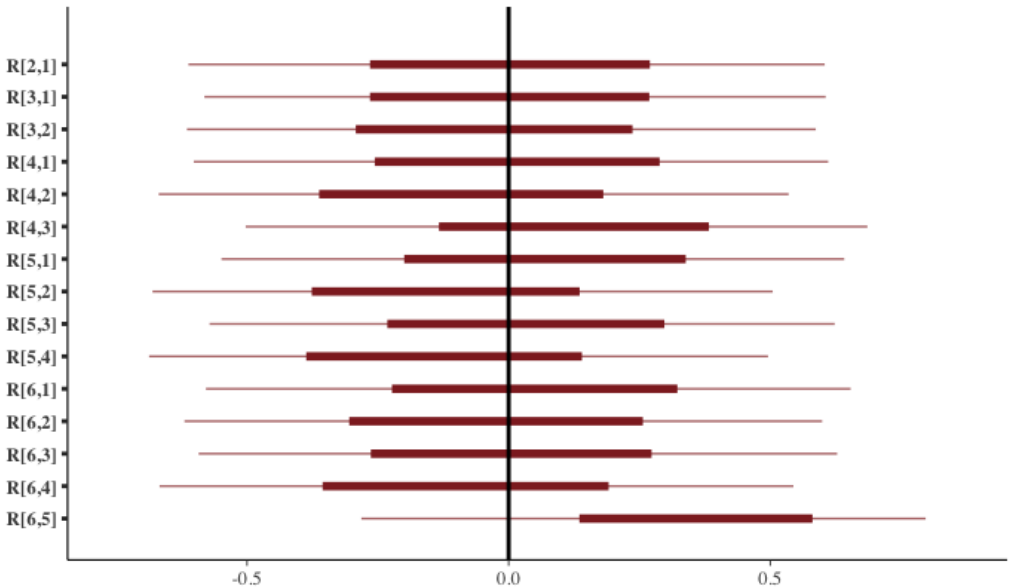


Figure 4: Pairwise correlation coefficient for all 6 effects.

Drug Preference Score

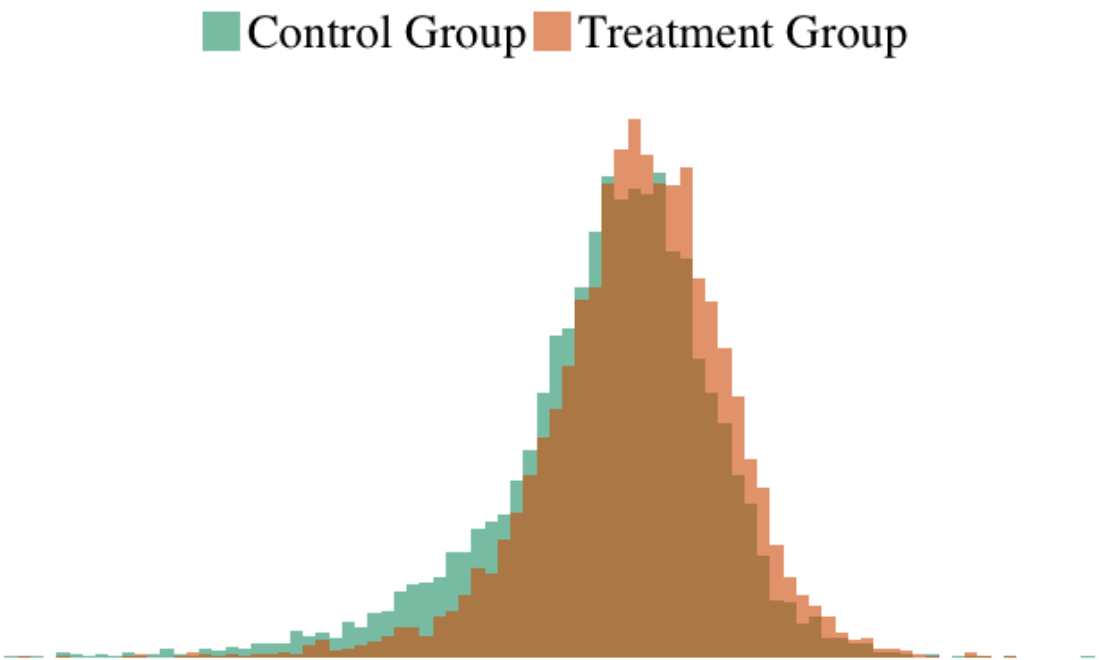
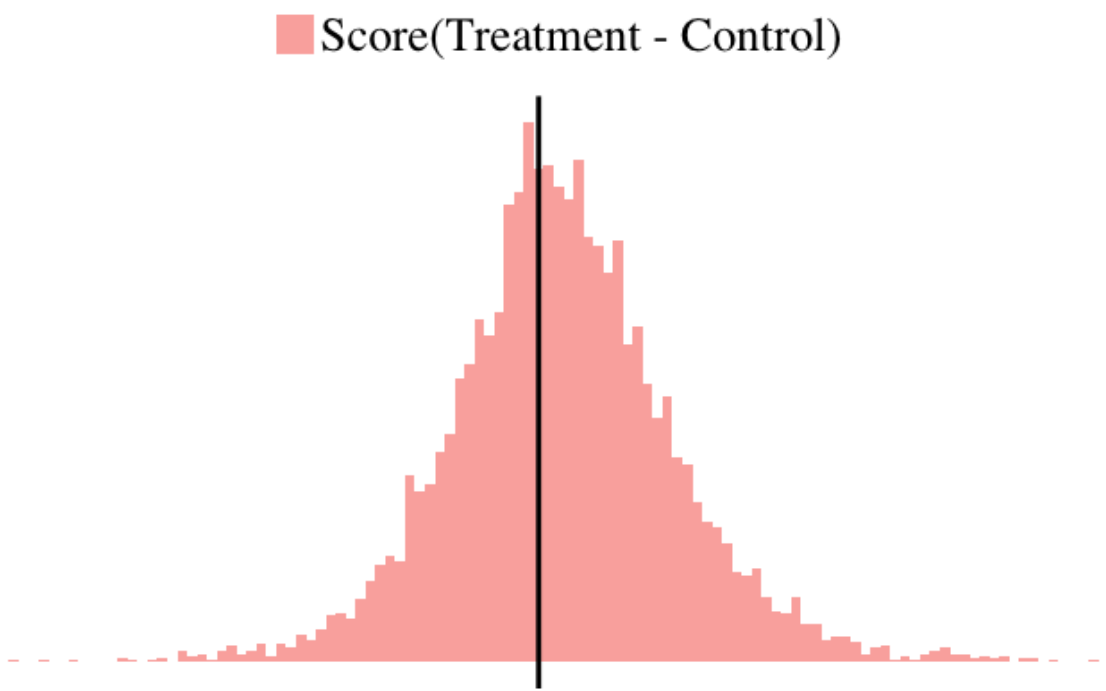


Figure 5: Final Score distribution s^T_{N+1} and s^C_{N+1} for a new individual taking the treatment (Rosiglitazone), and the placebo respectively.

Final Assessment

$$P(s^{\text{RSG}}_{N+1} > s^{C}_{N+1}) = 62\ \%$$



Thank you!

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