AIR-COPD Simulations

James Totterdell

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1 Model

For simplicity, the assumed model for Neutraphil Elastase (NE) at day 28 is

$$\log_{10}(Y_i) \sim \text{Normal}(\alpha + x_i^\mathsf{T}\beta, \sigma^2)$$

where β_p is the difference in mean NE under treatment $p \in \{1, 2, 3\}$ relative to control and x_i indicates the treatment received by participant i. Actual model would adjust for baseline NE and allow for multiple follow-up NE measurements (i.e. two measurements 7 days apart as indicated).

Treatments which reduce NE relative to control are considered promising. This is quantified by

$$P_p = \mathbb{P}(\beta_p < 0|y), p = 1, 2, 3.$$

and $P = (P_1, P_2, P_3)$.

The decision rules are

$$\begin{aligned}\phi_1(y) &= \mathbb{I}(P < \epsilon_0) \quad \text{(drop-out)} \\ \phi_2(y) &= \mathbb{I}(P > \epsilon_1) \quad \text{(graduate)}\end{aligned}$$

1.1 Priors

For model parameters, the following draft priors were specified (on $\log_{10} \mu$g/ml NE)

$$\begin{aligned}\alpha &\sim \text{Normal}(0.5, 0.5) \\ \beta &\sim \text{Normal}(0, 1) \\ \sigma^2 &\sim \text{Inverse-Gamma}(1.5, 6)\end{aligned}$$

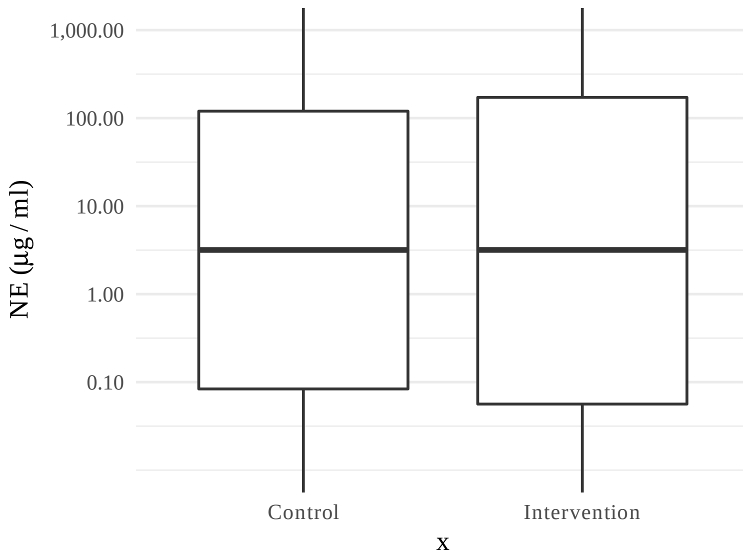

Figure 1: Prior predictive $\log_{10} \mu$g/ml NE assuming $\alpha \sim \text{Normal}(0.5, 0.5^2)$, $\beta \sim \text{Normal}(0, 1)$ and $\sigma^2 \sim \text{Inverse-Gamma}(1.5, 6)$.

2 Design

Initially, we only consider 3 investigational arms plus control. We assume the 3 active arms continue to receive participants until either the intervention is dropped-out, graduated, or the maximum sample size is reached.

An alternative would be to cap sample size on investigational arms (to 50?). E.g. an arm fails to "graduate" by 50 participants, then could potentially drop it out and introduce a new active treatment option. Maintaining 3 active investigational arms at all times. If a cap of 50, could assess futility by predictive probability of graduating an arm once 50 participants allocated to it.

3 Simulations

- Maximum sample size of 200 participants.
- Only 3 active arms plus control with no new arms introduced even if some active are dropped or graduate.
- No sample size cap is applied to active arms, e.g. if one arm is dropped the other arms may receive more than 50 participants up to the max of 200.
- effectiveness assessments after 100, 150, and 200 participants followed-up.

4 Example

```
## format_config (generic function with 1 method)
```

```
## 24×9 DataFrame
##  Row   trial  interim  arm    n       y_bar     mean_beta    sd_beta   P
##        Int64  Int64    Int64  Int64?  Float64?  Float64      Float64   Float64
##
##    1       1        1      1      25  0.360936   0.396267    0.190155  NaN
##    2       1        1      2      24  0.600181   0.194191    0.283703    0.246
##    3       1        1      3      25  0.488961   0.0884432   0.28069     0.376
##    4       1        1      4      26  0.435416   0.03742     0.277875    0.446
##    5       1        2      1      38  0.410749   0.426116    0.15736   NaN
##    6       1        2      2      36  0.474577   0.0469797   0.232033    0.419
##    7       1        2      3      37  0.551015   0.12118     0.230385    0.299
##    8       1        2      4      39  0.478331   0.0507375   0.227298    0.411
##
##   18       2        2      2      38  0.376148  -0.0646424   0.227213    0.611
##   19       2        2      3      37  0.429353  -0.012931    0.228761    0.522
##   20       2        2      4      38  0.326672  -0.11272     0.227213    0.690
##   21       2        3      1      49  0.435742   0.438112    0.1374    NaN
##   22       2        3      2      51  0.466716   0.0280193   0.196367    0.443
##   23       2        3      3      49  0.338506  -0.097488    0.19836     0.688
##   24       2        3      4      51  0.367707  -0.0689654   0.196367    0.637
##                                                       2 columns and 9 rows omitted
```

5 Operating Characteristics

epislon_0	epislon_1	nmax	beta	sigma	prior_sd_alpha	prior_sd_beta	prior_sigma
0.1	0.9	200	[0.0, 0.0, 0.0]	1	0.5	1.0	(1.5, 6.0)

Interim	Arm	$\mathbb{E}(n)$	$\mathbb{E}(\bar{y})$	$\mathbb{E}[\mathbb{E}[\beta\|y]]$	$\mathbb{E}[\phi_1(y)]$	$\mathbb{E}[\phi_2(y)]$
1	1	25.00	0.5	0.5	0.00	0.00
1	2	25.00	0.5	0.0	0.08	0.08
1	3	25.01	0.5	0.0	0.08	0.08
1	4	25.00	0.5	0.0	0.08	0.08
2	1	39.73	0.5	0.5	0.00	0.00
2	2	36.77	0.5	0.0	0.12	0.12
2	3	36.73	0.5	0.0	0.12	0.12
2	4	36.77	0.5	0.0	0.11	0.12
3	1	55.45	0.5	0.5	0.00	0.00
3	2	48.15	0.5	0.0	0.14	0.14
3	3	48.14	0.5	0.0	0.14	0.14
3	4	48.26	0.5	0.0	0.14	0.14

	epislon_0	epislon_1	nmax	beta	sigma	prior_sd_alpha	prior_sd_beta	prior_sigma
5	0.1	0.9	200	[-0.5, 0.0, 0.0]	1	0.5	1.0	(1.5, 6.0)

Interim	Arm	$\mathbb{E}(n)$	$\mathbb{E}(\bar{y})$	$\mathbb{E}[\mathbb{E}[\beta\|y]]$	$\mathbb{E}[\phi_1(y)]$	$\mathbb{E}[\phi_2(y)]$
1	1	25.00	0.50	0.48	0.00	0.00
1	2	25.00	0.00	-0.46	0.00	0.70
1	3	24.99	0.50	0.02	0.09	0.07
1	4	25.00	0.50	0.02	0.09	0.07
2	1	42.38	0.49	0.49	0.00	0.00
2	2	29.30	-0.02	-0.49	0.00	0.86
2	3	39.17	0.50	0.02	0.13	0.10
2	4	39.15	0.50	0.02	0.14	0.10
3	1	61.16	0.50	0.49	0.00	0.00
3	2	31.40	-0.02	-0.50	0.00	0.94
3	3	53.74	0.50	0.01	0.15	0.12
3	4	53.71	0.50	0.01	0.15	0.11

	epislon_0	epislon_1	nmax	beta	sigma	prior_sd_alpha	prior_sd_beta	prior_sigma
9	0.1	0.9	200	[-1.0, 0.0, 0.0]	1	0.5	1.0	(1.5, 6.0)

Interim	Arm	$\mathbb{E}(n)$	$\mathbb{E}(\bar{y})$	$\mathbb{E}[\mathbb{E}[\beta\|y]]$	$\mathbb{E}[\phi_1(y)]$	$\mathbb{E}[\phi_2(y)]$
1	1	25.00	0.5	0.47	0.00	0.00
1	2	25.00	-0.5	-0.93	0.00	0.99
1	3	25.00	0.5	0.03	0.10	0.07
1	4	25.00	0.5	0.03	0.10	0.07
2	1	43.86	0.5	0.48	0.00	0.00
2	2	25.13	-0.5	-0.94	0.00	1.00
2	3	40.57	0.5	0.02	0.13	0.09
2	4	40.44	0.5	0.02	0.13	0.09
3	1	63.46	0.5	0.49	0.00	0.00
3	2	25.08	-0.5	-0.95	0.00	1.00
3	3	55.79	0.5	0.01	0.15	0.11
3	4	55.67	0.5	0.01	0.15	0.11

	epislon_0	epislon_1	nmax	beta	sigma	prior_sd_alpha	prior_sd_beta	prior_sigma
13	0.1	0.9	200	[-0.5, -0.5, 0.0]	1	0.5	1.0	(1.5, 6.0)

Interim	Arm	$\mathbb{E}(n)$	$\mathbb{E}(\bar{y})$	$\mathbb{E}[\mathbb{E}[\beta\|y]]$	$\mathbb{E}[\phi_1(y)]$	$\mathbb{E}[\phi_2(y)]$
1	1	25.00	0.50	0.47	0.00	0.00
1	2	25.00	0.00	-0.45	0.00	0.69
1	3	25.00	0.00	-0.45	0.00	0.67
1	4	24.99	0.50	0.03	0.10	0.07
2	1	45.57	0.49	0.47	0.00	0.00
2	2	30.39	-0.02	-0.47	0.00	0.85
2	3	30.61	-0.02	-0.47	0.00	0.85
2	4	43.43	0.51	0.04	0.14	0.06
3	1	68.21	0.48	0.47	0.00	0.00
3	2	33.15	-0.02	-0.48	0.00	0.93
3	3	33.31	-0.03	-0.48	0.00	0.93
3	4	65.33	0.50	0.03	0.12	0.05