Osteoporosis Example

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Section 6 example

In a phase II clinical trial on an osteoporosis drug with two treatment groups (treatment and control), it was initially unclear whether the benefit of a new treatment over standard treatment would primarily be:
   (i) physiologic improvement of the knee, measured by joint space width (JSW) in mm,
   (ii) better pain relief, measured by a pain score, or
   (iii) better functional ability, measured by a function score.
Thus, the focus of this phase II trial was to establish a benefit in at least one of these indicators. A future phase III trial would then focus on the most promising variables.

Here, the hypothesis of interest is:

$$H_0 : \mu_{new} = \mu_{control}$$
$$H_1 : \mu_{new} > \mu_{control}$$

Follmann's method

Recreating author osteoporosis example (section 6). Numbers are a little different than mine, but they're close. (Edit: Confirmed with Glimm, these are correct).

Note: * F-stat off due to rounding * p-value is supposed to be halved since they double their significance level (e.g. if $\alpha = 0.05$, they would look for 2α, that's why it's under the subscript.)

```r
mean_diff <- matrix(c(0.35, - 2.4, -19.4), nrow = 1)
new <- matrix(c(0.38, 17, 43, 17, 2763, 3257, 43, 3257, 12042), nrow = 3)
old <- matrix( c(.17, 8.4, 20, 8.4, 2752, 2043, 20, 2043, 7572), nrow = 3)

my_pool_cov <- (31*new + 31*old)/(62)
author_pool_cov <- matrix(c(0.27, 12.7, 32, 12.7, 2758, 2758, 32, 2650, 9807),nrow = 3)

c <- (32 + 32 - 3 - 1)/(3 * (32 + 32 -1)) * (32*32)/(32+32)
my_stat <-  c * mean_diff %*% solve(my_pool_cov) %*% t(mean_diff)
author_stat <- c * mean_diff %*% solve(author_pool_cov) %*% t(mean_diff)

c(my_stat, author_stat)
```

```
## [1] 5.294320 5.553655
```

```r
pf(c(my_stat, author_stat), 3, 60, lower.tail = F)
```

```
## [1] 0.002638768 0.001975195
```

Authors F-stat is 5.37 and corresponding p-value of 0.0024, which is the result from :

```
pf(5.37, 3, 60, lower.tail = F)
```

[1] 0.00242433

But this p-value should be divide by 2 since the significance level is doubled (Confirmed with Author)

Glimm's Method

```
min_mu_obj <- function(mu, G, mean_diff){
x_bar <- matrix(mu, nrow = 1)  - mean_diff
(32 + 32 - 3 - 1)/(3 * (32 + 32 -1)) * (32*32)/(32+32) * x_bar %*% solve(G) %*% t(x_bar)
}


ex_val <- optim(par = rep(0,3),
                fn = min_mu_obj,
                upper = rep(0,3),
                method = "L-BFGS-B",
                mean_diff = mean_diff,
                G = my_pool_cov)

#output of the optimization function (minimized when mu = par)
ex_val
```

```
## $par
## [1]   0.00000 -18.56364 -59.49091
##
## $value
## [1] 2.262626
##
## $counts
## function gradient
##       18       18
##
## $convergence
## [1] 0
##
## $message
## [1] "CONVERGENCE: REL_REDUCTION_OF_F <= FACTR*EPSMCH"
```

```
#p-value
pf(ex_val$value, df1 = 3,df2 =  32+32-3-1, lower.tail = F)
```

[1] 0.09032091

These results basically match, who found optimal value of (0, -18.4, -59.5) and a F-statistic of 2.27, with corresponding p-value of 0.0447. Here the p-value is halved.