Bayesian Sample Size simulations

Vahan Aslanyan

Lecanemab

From study protocol:

"The sample size for this study is estimated based on comparison of BAN2401 versus placebo with respect to the primary efficacy endpoint, the change from baseline in CDR-SB at 18 months. Based on data from BAN2401 Phase 2 study BAN2401-G000-201, an estimated standard deviation of the change from baseline CDR-SB at 18 months in placebo is 2.031 and an estimated treatment difference is 0.373 in all subjects. Therefore, assuming an estimated 20% dropout rate at 18 months in this study, a total sample size of 1566 subjects, including 783 subjects in placebo and 783 subjects in BAN2401, will have 90% power to detect the treatment difference between BAN2401 and placebo in all subjects using a 2-sample t-test at a significance level of 2-sided alpha = 0.05."

From sample size rationale: sd=2.031 variance is 4.124961, so nu_prior is 0.2424265 , so alpha/beta is 0.2424265

From collected data: SE=0.1122449 N=1795 , so SD=4.755529 (SE*sqrt(N)), Mean Change=0.45, so treatment effect size is 0.0946267

```
set.seed(219)
source("bayesian_ssr.R")
```

```
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()
alpha<-1:10000
beta<-round(alpha/0.2424265)
for(i in 1:1000){
```

```
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95,zeta=0.90,xi=0.95,r=c(0.5,0.5),
                               q_prior=c(1,1),delta_star=0.373)
  if(any(is.na(aux)))next
  yE_aux=rnorm(round(aux$treatment1/2),mean=0.45, sd=4.755529)
  yC_aux=rnorm(round(aux$treatment2/2),mean=0, sd=4.755529)
  y=c(yC_aux,yE_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/2)),
                          rep(2,round(aux$treatment2/2)))
  df=tibble(treatment_assignment,y)
  aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                   q_prior=c(0.5,0.5),mu_prior =c(0,0),
                                   N_treat = c(round(aux$treatment1/2),
                                               round(aux$treatment2/2)),
                                   y_treatment = df)
  df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,
                               aux_post$q_andmu_posteriors)
  df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,
                                  aux_post$alpha_beta_params)
  df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
  df_sample_size<-rbind(df_sample_size,aux)
  treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                  aux_post$D,
                                                  aux_post$alpha_beta_params)
  new_r<-allocation_calculation(treatment_differences)
  interim_allocation<-rbind(interim_allocation,new_r)
}

colnames(interim_allocation)<-paste0("r", seq_along(new_r))
colMeans(df_sample_size)
```

```
treatment1 treatment2
   515.889    515.889
```

```
interim_ss<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,
```

```
                                        xi=0.95,r=c(0.5,0.5),
                                        q_prior =as.numeric(df_q_andmu_posteriors[i,grep("q
                                        delta_star=0.373)
    interim_ss<-rbind(interim_ss,interim_aux)
  }

  colMeans(interim_ss)
```

```
treatment1 treatment2
  479.9325   479.9325
```

```
  interim_ss_rar<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                        beta_prior = df_alpha_beta_posteriors$beta_posterio
                                        eta=0.95, zeta=0.90,
                                        xi=0.95,r=as.numeric(interim_allocation[i,]),
                                        q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                        delta_star=0.373)
    interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
  }
  colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2
  473.8031   531.8108
```

```
  colMeans(interim_allocation)
```

```
       r1        r2
0.4614618 0.5385382
```

Whitehead et al. 2015

Taken from

Carlsen JE, Køber L, Torp-Pedersen C, Johansen P. Relation between dose of bendrofluazide, antihypertensive effect, andadverse biochemical effects.British Medical Journal1990;300:975–978.

```r
alpha<-1:10000
beta<-round(alpha/0.0204)
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()


for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/3,1/6,1/6,1/6,1/6),
                               q_prior=c(10,2,2,2,2),delta_star=5)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/2),mean=2.8, sd=12.3)
  y2_aux=rnorm(round(aux$treatment2/2),mean=12.7, sd=14.1)
  y3_aux=rnorm(round(aux$treatment3/2),mean=14.3, sd=11.5)
  y4_aux=rnorm(round(aux$treatment4/2),mean=13.4, sd=14.4)
  y5_aux=rnorm(round(aux$treatment5/2),mean=17, sd=15)

  y=c(y1_aux,y2_aux,y3_aux,y4_aux,y5_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/2)),
                          rep(2,round(aux$treatment2/2)),
                          rep(3,round(aux$treatment3/2)),
                          rep(4,round(aux$treatment4/2)),
                          rep(5,round(aux$treatment5/2)))
  df=tibble(treatment_assignment,y)
  aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                   q_prior=c(10,2,2,2,2),
                                   N_treat = c(round(aux$treatment1/2),
                                               round(aux$treatment2/2),
                                               round(aux$treatment3/2),
                                               round(aux$treatment4/2),
                                               round(aux$treatment5/2)),
                                   y_treatment = df)
  df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,
                               aux_post$q_andmu_posteriors)
```

```
    df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,
                                    aux_post$alpha_beta_params)
    df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
    df_sample_size<-rbind(df_sample_size,aux)
    treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                    aux_post$D,
                                                    aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4 treatment5
    45.132     22.566     22.566     22.566     22.566
```

```
  interim_ss<-tibble()
  for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posterior
                                       beta_prior = df_alpha_beta_posteriors$beta_posterior[
                                       eta=0.95, zeta=0.90,xi=0.95,
                                       r=c(1/3,1/6,1/6,1/6,1/6),
                                       q_prior =as.numeric(df_q_andmu_posteriors[i,grep("q",
                                       delta_star=5)
    interim_ss<-rbind(interim_ss,interim_aux)
  }

  colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4 treatment5
  25.82833   12.91417   12.91417   12.91417   12.91417
```

```
  interim_ss_rar<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,xi=0.95,
                                         r=as.numeric(interim_allocation[i,]),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
```

```
                                          delta_star=5)
    interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
  }

  colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4 treatment5
  9.344251  20.508666  22.033935  20.735637  22.011144
```

```
  colnames(interim_allocation)<-paste0("r", seq_along(new_r))
  colMeans(interim_allocation)
```

```
        r1         r2         r3         r4         r5
0.09684886 0.22133478 0.22877208 0.22406380 0.22898049
```

Hypothetical Scenario #1

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.2. One interim analysis at 50% recruited

```
  alpha<-1:10000
  beta<-alpha
  df_sample_size<-tibble()
  df_posteriors<-tibble()
  df_q_andmu_posteriors<-tibble()
  df_alpha_beta_posteriors<-tibble()
  df_D_posteriors<-tibble()
  interim_allocation<-tibble()


  for(i in 1:1000){
    alpha1<-sample(alpha,1)
    beta1<-beta[alpha1==alpha]
    aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                                 eta=0.95, zeta=0.90,
                                 xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                 q_prior=c(2,2,2,2),delta_star=0.2)
    if(any(is.na(aux)))next
    y1_aux=rnorm(round(aux$treatment1/2),mean=0, sd=1)
```

```
    y2_aux=rnorm(round(aux$treatment2/2),mean=0.1, sd=1)
    y3_aux=rnorm(round(aux$treatment3/2),mean=0.2, sd=1)
    y4_aux=rnorm(round(aux$treatment4/2),mean=0.6, sd=1)

    y=c(y1_aux,y2_aux,y3_aux,y4_aux)
    treatment_assignment<-c(rep(1,round(aux$treatment1/2)),
                            rep(2,round(aux$treatment2/2)),
                            rep(3,round(aux$treatment3/2)),
                            rep(4,round(aux$treatment4/2)))
    df=tibble(treatment_assignment,y)
    aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                     q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                     N_treat = c(round(aux$treatment1/2),
                                                 round(aux$treatment2/2),
                                                 round(aux$treatment3/2),
                                                 round(aux$treatment4/2)),
                                                 y_treatment = df)
    df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,aux_post$q_andmu_posteriors)
    df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,aux_post$alpha_beta_params)
    df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
    df_sample_size<-rbind(df_sample_size,aux)
    treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                    aux_post$D,
                                                    aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4
  434.6977   434.6977   434.6977   434.6977
```

```
  interim_ss<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,
                                         xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                         delta_star=0.2)
```

```
  interim_ss<-rbind(interim_ss,interim_aux)
}

colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4
  213.0592   213.0592   213.0592   213.0592
```

```
colnames(interim_allocation)<-paste0("r", seq_along(new_r))
colMeans(interim_allocation)
```

```
       r1        r2        r3        r4
0.1578636 0.2352264 0.2911887 0.3157213
```

```
interim_ss_rar<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,xi=0.95,
                                       r=as.numeric(interim_allocation[i,]),
                                       q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                       delta_star=0.2)
  interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
}

colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  187.8111   262.5516   342.8776   375.9317
```

Hypothetical Scenario #2

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.2. One interim analysis at 25% recruited

```
alpha<-1:10000
beta<-alpha
```

```r
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()


for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/4,1/4,1/4,1/4),
                               q_prior=c(2,2,2,2),delta_star=0.2)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/4),mean=0, sd=1)
  y2_aux=rnorm(round(aux$treatment2/4),mean=0.1, sd=1)
  y3_aux=rnorm(round(aux$treatment3/4),mean=0.2, sd=1)
  y4_aux=rnorm(round(aux$treatment4/4),mean=0.6, sd=1)

  y=c(y1_aux,y2_aux,y3_aux,y4_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/4)),
                          rep(2,round(aux$treatment2/4)),
                          rep(3,round(aux$treatment3/4)),
                          rep(4,round(aux$treatment4/4)))
  df=tibble(treatment_assignment,y)
  aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                   q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                   N_treat=c(round(aux$treatment1/4),
                                             round(aux$treatment2/4),
                                             round(aux$treatment3/4),
                                             round(aux$treatment4/4)),
                                   y_treatment = df)
  df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,aux_post$q_andmu_posteriors)
  df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,aux_post$alpha_beta_params)
  df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
  df_sample_size<-rbind(df_sample_size,aux)
  treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                  aux_post$D,
                                                  aux_post$alpha_beta_params)
```

```
    new_r<-allocation_calculation(treatment_differences,n=1,N=4)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4
   435.068    435.068    435.068    435.068
```

```
  interim_ss<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,
                                         xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                         delta_star=0.2)
    interim_ss<-rbind(interim_ss,interim_aux)
  }

  colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4
  323.3542   323.3542   323.3542   323.3542
```

```
  colnames(interim_allocation)<-paste0("r", seq_along(new_r))
  colMeans(interim_allocation)
```

```
       r1        r2        r3        r4
0.2077456 0.2338848 0.2645468 0.2938228
```

```
  interim_ss_rar<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,
                                         xi=0.95,r=as.numeric(interim_allocation[i,]),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
```

```
                                          delta_star=0.2)
  interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
}

colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  320.8438   350.9073   405.9225   453.7673
```

Hypothetical Scenario #3

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.2. One interim analysis at 12.5% recruited

```
alpha<-1:10000
beta<-alpha
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()


for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/4,1/4,1/4,1/4),
                               q_prior=c(2,2,2,2),delta_star=0.2)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/8),mean=0, sd=1)
  y2_aux=rnorm(round(aux$treatment2/8),mean=0.1, sd=1)
  y3_aux=rnorm(round(aux$treatment3/8),mean=0.2, sd=1)
  y4_aux=rnorm(round(aux$treatment4/8),mean=0.6, sd=1)

  y=c(y1_aux,y2_aux,y3_aux,y4_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/8)),
                          rep(2,round(aux$treatment2/8)),
```

```
                          rep(3,round(aux$treatment3/8)),
                          rep(4,round(aux$treatment4/8)))
    df=tibble(treatment_assignment,y)
    aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                     q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                     N_treat=c(round(aux$treatment1/8),
                                               round(aux$treatment2/8),
                                               round(aux$treatment3/8),
                                               round(aux$treatment4/8)),
                                     y_treatment = df)
    df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,aux_post$q_andmu_posteriors)
    df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,aux_post$alpha_beta_params)
    df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
    df_sample_size<-rbind(df_sample_size,aux)
    treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                    aux_post$D,
                                                    aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences,n=1,N=8)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4
  433.9355   433.9355   433.9355   433.9355
```

```
  interim_ss<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,
                                         xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                         delta_star=0.2)
    interim_ss<-rbind(interim_ss,interim_aux)
  }

  colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4
   377.904    377.904    377.904    377.904
```

```
colnames(interim_allocation)<-paste0("r", seq_along(new_r))
colMeans(interim_allocation)
```

```
      r1        r2        r3        r4
0.2325178 0.2392200 0.2529268 0.2753354
```

```
interim_ss_rar<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,
                                       xi=0.95,r=as.numeric(interim_allocation[i,]),
                                       q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                       delta_star=0.2)
  interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
}

colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  381.7728   390.1089   414.3149   451.9974
```

Hypothetical Scenario #4

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.3. One interim analysis at 50% recruited

```
alpha<-1:10000
beta<-alpha
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()


for(i in 1:1000){
  alpha1<-sample(alpha,1)
```

```
    beta1<-beta[alpha1==alpha]
    aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                                 eta=0.95, zeta=0.90,
                                 xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                 q_prior=c(2,2,2,2),delta_star=0.3)
    if(any(is.na(aux)))next
    y1_aux=rnorm(round(aux$treatment1/2),mean=0, sd=1)
    y2_aux=rnorm(round(aux$treatment2/2),mean=0.1, sd=1)
    y3_aux=rnorm(round(aux$treatment3/2),mean=0.2, sd=1)
    y4_aux=rnorm(round(aux$treatment4/2),mean=0.6, sd=1)

    y=c(y1_aux,y2_aux,y3_aux,y4_aux)
    treatment_assignment<-c(rep(1,round(aux$treatment1/2)),
                            rep(2,round(aux$treatment2/2)),
                            rep(3,round(aux$treatment3/2)),
                            rep(4,round(aux$treatment4/2)))
    df=tibble(treatment_assignment,y)
    aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                     q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                     N_treat = c(round(aux$treatment1/2),
                                                 round(aux$treatment2/2),
                                                 round(aux$treatment3/2),
                                                 round(aux$treatment4/2)),
                                                 y_treatment = df)
    df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,aux_post$q_andmu_posteriors)
    df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,aux_post$alpha_beta_params)
    df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
    df_sample_size<-rbind(df_sample_size,aux)
    treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                    aux_post$D,
                                                    aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4
  191.9923   191.9923   191.9923   191.9923
```

```r
interim_ss<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,
                                       xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                       q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                       delta_star=0.3)
  interim_ss<-rbind(interim_ss,interim_aux)
}

colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4
    94.003     94.003     94.003     94.003
```

```r
colnames(interim_allocation)<-paste0("r", seq_along(new_r))
colMeans(interim_allocation)
```

```
       r1        r2        r3        r4
0.1691456 0.2201511 0.2737260 0.3369774
```

```r
interim_ss_rar<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,xi=0.95,
                                       r=as.numeric(interim_allocation[i,]),
                                       q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                       delta_star=0.3)
  interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
}

colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  97.91523  111.19541  149.51165  193.70871
```

Hypothetical Scenario #5

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.3. One interim analysis at 25% recruited

```
alpha<-1:10000
beta<-alpha
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()


for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/4,1/4,1/4,1/4),
                               q_prior=c(2,2,2,2),delta_star=0.3)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/4),mean=0, sd=1)
  y2_aux=rnorm(round(aux$treatment2/4),mean=0.1, sd=1)
  y3_aux=rnorm(round(aux$treatment3/4),mean=0.2, sd=1)
  y4_aux=rnorm(round(aux$treatment4/4),mean=0.6, sd=1)

  y=c(y1_aux,y2_aux,y3_aux,y4_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/4)),
                          rep(2,round(aux$treatment2/4)),
                          rep(3,round(aux$treatment3/4)),
                          rep(4,round(aux$treatment4/4)))
  df=tibble(treatment_assignment,y)
  aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                   q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                   N_treat=c(round(aux$treatment1/4),
                                             round(aux$treatment2/4),
                                             round(aux$treatment3/4),
                                             round(aux$treatment4/4)),
                                   y_treatment = df)
```

```
    df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,aux_post$q_andmu_posteriors)
    df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,aux_post$alpha_beta_params)
    df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
    df_sample_size<-rbind(df_sample_size,aux)
    treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                    aux_post$D,
                                                    aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences,n=1,N=4)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4
  191.3226   191.3226   191.3226   191.3226
```

```
  interim_ss<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,
                                         xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                         delta_star=0.3)
    interim_ss<-rbind(interim_ss,interim_aux)
  }

  colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4
  142.6089   142.6089   142.6089   142.6089
```

```
  colnames(interim_allocation)<-paste0("r", seq_along(new_r))
  colMeans(interim_allocation)
```

```
       r1        r2        r3        r4
0.2161801 0.2278106 0.2539584 0.3020509
```

```
interim_ss_rar<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,
                                       xi=0.95,r=as.numeric(interim_allocation[i,]),
                                       q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                       delta_star=0.3)
  interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
}

colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  149.3803   153.0989   173.0991   208.5789
```

Hypothetical Scenario #6

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.3. One interim analysis at 12.5% recruited

```
alpha<-1:10000
beta<-alpha
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation<-tibble()


for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/4,1/4,1/4,1/4),
                               q_prior=c(2,2,2,2),delta_star=0.3)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/8),mean=0, sd=1)
```

```
    y2_aux=rnorm(round(aux$treatment2/8),mean=0.1, sd=1)
    y3_aux=rnorm(round(aux$treatment3/8),mean=0.2, sd=1)
    y4_aux=rnorm(round(aux$treatment4/8),mean=0.6, sd=1)

    y=c(y1_aux,y2_aux,y3_aux,y4_aux)
    treatment_assignment<-c(rep(1,round(aux$treatment1/8)),
                            rep(2,round(aux$treatment2/8)),
                            rep(3,round(aux$treatment3/8)),
                            rep(4,round(aux$treatment4/8)))
    df=tibble(treatment_assignment,y)
    aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                     q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                     N_treat=c(round(aux$treatment1/8),
                                               round(aux$treatment2/8),
                                               round(aux$treatment3/8),
                                               round(aux$treatment4/8)),
                                     y_treatment = df)
    df_q_andmu_posteriors<-rbind(df_q_andmu_posteriors,aux_post$q_andmu_posteriors)
    df_alpha_beta_posteriors<-rbind(df_alpha_beta_posteriors,aux_post$alpha_beta_params)
    df_D_posteriors<-rbind(df_D_posteriors,aux_post$D)
    df_sample_size<-rbind(df_sample_size,aux)
    treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                    aux_post$D,
                                                    aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences,n=1,N=8)
    interim_allocation<-rbind(interim_allocation,new_r)
    #df_posteriors<-rbind(df_posteriors,aux_post)
  }
  colMeans(df_sample_size)
```

```
treatment1 treatment2 treatment3 treatment4
   192.048    192.048    192.048    192.048
```

```
  interim_ss<-tibble()
  for(i in 1:nrow(df_sample_size)){
    interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                         beta_prior = df_alpha_beta_posteriors$beta_posterio
                                         eta=0.95, zeta=0.90,
                                         xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                         q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                         delta_star=0.3)
```

```
  interim_ss<-rbind(interim_ss,interim_aux)
}

colMeans(interim_ss)
```

```
treatment1 treatment2 treatment3 treatment4
  166.8262   166.8262   166.8262   166.8262
```

```
colnames(interim_allocation)<-paste0("r", seq_along(new_r))
colMeans(interim_allocation)
```

```
       r1        r2        r3        r4
0.2380354 0.2370419 0.2498226 0.2751002
```

```
interim_ss_rar<-tibble()
for(i in 1:nrow(df_sample_size)){
  interim_aux<-sample_size_calculation(alpha_prior =df_alpha_beta_posteriors$alpha_posteri
                                       beta_prior = df_alpha_beta_posteriors$beta_posterio
                                       eta=0.95, zeta=0.90,
                                       xi=0.95,r=as.numeric(interim_allocation[i,]),
                                       q_prior =as.numeric( df_q_andmu_posteriors[i,grep("
                                       delta_star=0.3)
  interim_ss_rar<-rbind(interim_ss_rar,interim_aux)
}

colMeans(interim_ss_rar,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  172.9178   170.9255   180.8570   199.7207
```

Hypothetical Scenario #7

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.2. One interim analysis at 25% recruited another at 50% recruited

```
alpha<-1:10000
beta<-alpha
```

```r
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation_1<-tibble()
interim_ss_rar_1<-tibble()
interim_allocation_2<-tibble()
interim_ss_rar_2<-tibble()
for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/4,1/4,1/4,1/4),
                               q_prior=c(2,2,2,2),delta_star=0.2)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/4),mean=0, sd=1)
  y2_aux=rnorm(round(aux$treatment2/4),mean=0.1, sd=1)
  y3_aux=rnorm(round(aux$treatment3/4),mean=0.2, sd=1)
  y4_aux=rnorm(round(aux$treatment4/4),mean=0.6, sd=1)

  y=c(y1_aux,y2_aux,y3_aux,y4_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/4)),
                          rep(2,round(aux$treatment2/4)),
                          rep(3,round(aux$treatment3/4)),
                          rep(4,round(aux$treatment4/4)))
  df=tibble(treatment_assignment,y)
  aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                   q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                   N_treat = c(round(aux$treatment1/4),
                                               round(aux$treatment2/4),
                                               round(aux$treatment3/4),
                                               round(aux$treatment4/4)),
                                               y_treatment = df)
  treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                  aux_post$D,
                                                  aux_post$alpha_beta_params)
  new_r<-allocation_calculation(treatment_differences)
  interim_allocation_1<-rbind(interim_allocation_1,new_r)
  df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
```

```
interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_poste
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                     eta=0.95, zeta=0.90,xi=0.95,
                                     r=new_r,
                                     q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                     delta_star=0.2)
interim_ss_rar_1<-rbind(interim_ss_rar_1,interim_aux)
if(any(is.na(interim_aux)))next
y1_aux=rnorm(max(round((interim_aux$treatment1/2-aux$treatment1/4)),1),mean=0, sd=1)
y2_aux=rnorm(max(round((interim_aux$treatment2/2-aux$treatment2/4)),1),mean=0.1, sd=1)
y3_aux=rnorm(max(round((interim_aux$treatment3/2-aux$treatment3/4)),1),mean=0.2, sd=1)
y4_aux=rnorm(max(round((interim_aux$treatment4/2-aux$treatment4/4)),1),mean=0.6, sd=1)
y_aux=c(y1_aux,y2_aux,y3_aux,y4_aux)
treatment_assignment<-c(rep(1,max(round((interim_aux$treatment1/2-aux$treatment1/4)),1))
                        rep(2,max(round((interim_aux$treatment2/2-aux$treatment2/4)),1))
                        rep(3,max(round((interim_aux$treatment3/2-aux$treatment3/4)),1))
                        rep(4,max(round((interim_aux$treatment4/2-aux$treatment4/4)),1))
 df_aux=tibble(treatment_assignment,y=y_aux)
 df<-rbind(df,df_aux)
 df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
 aux_post<-posterior_calculations(alpha_prior =aux_post$alpha_beta_params$alpha_posterio
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                  q_prior =as.numeric( df_q_andmu_posteriors[,grep("q",co
                                  mu_prior= as.numeric( df_q_andmu_posteriors[,grep("mu",
                                  N_treat = c(round(interim_aux$treatment1/2),
                                              round(interim_aux$treatment2/2),
                                              round(interim_aux$treatment3/2),
                                              round(interim_aux$treatment4/2)),
                                              y_treatment = df)
  treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                  aux_post$D,
                                                  aux_post$alpha_beta_params)
 new_r<-allocation_calculation(treatment_differences)
 interim_allocation_2<-rbind(interim_allocation_2,new_r)
 df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
 interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_post
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                     eta=0.95, zeta=0.90,xi=0.95,
                                     r=new_r,
                                     q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                     delta_star=0.2)
```

```
    interim_ss_rar_2<-rbind(interim_ss_rar_2,interim_aux)
  }
  colMeans(interim_ss_rar_2,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  157.6293   199.8687   286.9638   314.9156
```

Hypothetical Scenario #8

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.3. One interim analysis at 25% recruited another at 50% recruited

```
  alpha<-1:10000
  beta<-alpha
  df_sample_size<-tibble()
  df_posteriors<-tibble()
  df_q_andmu_posteriors<-tibble()
  df_alpha_beta_posteriors<-tibble()
  df_D_posteriors<-tibble()
  interim_allocation_1<-tibble()
  interim_ss_rar_1<-tibble()
  interim_allocation_2<-tibble()
  interim_ss_rar_2<-tibble()
  for(i in 1:1000){
    alpha1<-sample(alpha,1)
    beta1<-beta[alpha1==alpha]
    aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                                 eta=0.95, zeta=0.90,
                                 xi=0.95,r=c(1/4,1/4,1/4,1/4),
                                 q_prior=c(2,2,2,2),delta_star=0.3)
    if(any(is.na(aux)))next
    y1_aux=rnorm(round(aux$treatment1/4),mean=0, sd=1)
    y2_aux=rnorm(round(aux$treatment2/4),mean=0.1, sd=1)
    y3_aux=rnorm(round(aux$treatment3/4),mean=0.2, sd=1)
    y4_aux=rnorm(round(aux$treatment4/4),mean=0.6, sd=1)

    y=c(y1_aux,y2_aux,y3_aux,y4_aux)
    treatment_assignment<-c(rep(1,round(aux$treatment1/4)),
                            rep(2,round(aux$treatment2/4)),
                            rep(3,round(aux$treatment3/4)),
```

```
                        rep(4,round(aux$treatment4/4)))
df=tibble(treatment_assignment,y)
aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                 q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                 N_treat = c(round(aux$treatment1/4),
                                             round(aux$treatment2/4),
                                             round(aux$treatment3/4),
                                             round(aux$treatment4/4)),
                                             y_treatment = df)
treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                aux_post$D,
                                                aux_post$alpha_beta_params)
new_r<-allocation_calculation(treatment_differences)
interim_allocation_1<-rbind(interim_allocation_1,new_r)
df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_poste
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                     eta=0.95, zeta=0.90,xi=0.95,
                                     r=new_r,
                                     q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                     delta_star=0.3)
interim_ss_rar_1<-rbind(interim_ss_rar_1,interim_aux)
if(any(is.na(interim_aux)))next
y1_aux=rnorm(max(round((interim_aux$treatment1/2-aux$treatment1/4)),1),mean=0, sd=1)
y2_aux=rnorm(max(round((interim_aux$treatment2/2-aux$treatment2/4)),1),mean=0.1, sd=1)
y3_aux=rnorm(max(round((interim_aux$treatment3/2-aux$treatment3/4)),1),mean=0.2, sd=1)
y4_aux=rnorm(max(round((interim_aux$treatment4/2-aux$treatment4/4)),1),mean=0.6, sd=1)
y_aux=c(y1_aux,y2_aux,y3_aux,y4_aux)
treatment_assignment<-c(rep(1,max(round((interim_aux$treatment1/2-aux$treatment1/4)),1))
                        rep(2,max(round((interim_aux$treatment2/2-aux$treatment2/4)),1))
                        rep(3,max(round((interim_aux$treatment3/2-aux$treatment3/4)),1))
                        rep(4,max(round((interim_aux$treatment4/2-aux$treatment4/4)),1))
 df_aux=tibble(treatment_assignment,y=y_aux)
 df<-rbind(df,df_aux)
 df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
 aux_post<-posterior_calculations(alpha_prior =aux_post$alpha_beta_params$alpha_posterio
                                      beta_prior = aux_post$alpha_beta_params$beta_poster
                                 q_prior =as.numeric( df_q_andmu_posteriors[,grep("q",co
                                 mu_prior= as.numeric( df_q_andmu_posteriors[,grep("mu",
                                 N_treat = c(round(interim_aux$treatment1/2),
                                             round(interim_aux$treatment2/2),
```

```
                                                round(interim_aux$treatment3/2),
                                                round(interim_aux$treatment4/2)),
                                                y_treatment = df)
     treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                     aux_post$D,
                                                     aux_post$alpha_beta_params)
    new_r<-allocation_calculation(treatment_differences)
    interim_allocation_2<-rbind(interim_allocation_2,new_r)
    df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
    interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_post
                                         beta_prior = aux_post$alpha_beta_params$beta_poster
                                         eta=0.95, zeta=0.90,xi=0.95,
                                         r=new_r,
                                         q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                         delta_star=0.3)
    interim_ss_rar_2<-rbind(interim_ss_rar_2,interim_aux)
  }
  colMeans(interim_ss_rar_2,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  86.01633   87.68924  134.96192  171.87960
```

Hypothetical Scenario #9

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.3. One interim analysis at 25% recruited another at 75% recruited

```
  alpha<-1:10000
  beta<-alpha
  df_sample_size<-tibble()
  df_posteriors<-tibble()
  df_q_andmu_posteriors<-tibble()
  df_alpha_beta_posteriors<-tibble()
  df_D_posteriors<-tibble()
  interim_allocation_1<-tibble()
  interim_ss_rar_1<-tibble()
  interim_allocation_2<-tibble()
  interim_ss_rar_2<-tibble()
  for(i in 1:1000){
    alpha1<-sample(alpha,1)
```

```
beta1<-beta[alpha1==alpha]
aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                             eta=0.95, zeta=0.90,
                             xi=0.95,r=c(1/4,1/4,1/4,1/4),
                             q_prior=c(2,2,2,2),delta_star=0.3)
if(any(is.na(aux)))next
y1_aux=rnorm(round(aux$treatment1/4),mean=0, sd=1)
y2_aux=rnorm(round(aux$treatment2/4),mean=0.1, sd=1)
y3_aux=rnorm(round(aux$treatment3/4),mean=0.2, sd=1)
y4_aux=rnorm(round(aux$treatment4/4),mean=0.6, sd=1)

y=c(y1_aux,y2_aux,y3_aux,y4_aux)
treatment_assignment<-c(rep(1,round(aux$treatment1/4)),
                        rep(2,round(aux$treatment2/4)),
                        rep(3,round(aux$treatment3/4)),
                        rep(4,round(aux$treatment4/4)))
df=tibble(treatment_assignment,y)
aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                 q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                 N_treat = c(round(aux$treatment1/4),
                                             round(aux$treatment2/4),
                                             round(aux$treatment3/4),
                                             round(aux$treatment4/4)),
                                             y_treatment = df)
treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                aux_post$D,
                                                aux_post$alpha_beta_params)
new_r<-allocation_calculation(treatment_differences)
interim_allocation_1<-rbind(interim_allocation_1,new_r)
df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_poste
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                     eta=0.95, zeta=0.90,xi=0.95,
                                     r=new_r,
                                     q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                     delta_star=0.3)
interim_ss_rar_1<-rbind(interim_ss_rar_1,interim_aux)
if(any(is.na(interim_aux)))next
y1_aux=rnorm(max(round((interim_aux$treatment1*0.75-aux$treatment1/4)),1),mean=0, sd=1)
y2_aux=rnorm(max(round((interim_aux$treatment2*0.75-aux$treatment2/4)),1),mean=0.1, sd=1
y3_aux=rnorm(max(round((interim_aux$treatment3*0.75-aux$treatment3/4)),1),mean=0.2, sd=1
```

```
    y4_aux=rnorm(max(round((interim_aux$treatment4*0.75-aux$treatment4/4)),1),mean=0.6, sd=1
    y_aux=c(y1_aux,y2_aux,y3_aux,y4_aux)
    treatment_assignment<-c(rep(1,max(round((interim_aux$treatment1*0.75-aux$treatment1/4)),
                            rep(2,max(round((interim_aux$treatment2*0.75-aux$treatment2/4)),
                            rep(3,max(round((interim_aux$treatment3*0.75-aux$treatment3/4)),
                            rep(4,max(round((interim_aux$treatment4*0.75-aux$treatment4/4)),
     df_aux=tibble(treatment_assignment,y=y_aux)
     df<-rbind(df,df_aux)
     df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
     aux_post<-posterior_calculations(alpha_prior =aux_post$alpha_beta_params$alpha_posterio
                                      beta_prior = aux_post$alpha_beta_params$beta_poster
                                    q_prior =as.numeric( df_q_andmu_posteriors[,grep("q",co
                                    mu_prior= as.numeric( df_q_andmu_posteriors[,grep("mu",
                                    N_treat = c(round(interim_aux$treatment1*0.75),
                                                round(interim_aux$treatment2*0.75),
                                                round(interim_aux$treatment3*0.75),
                                                round(interim_aux$treatment4*0.75)),
                                                y_treatment = df)
      treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                      aux_post$D,
                                                      aux_post$alpha_beta_params)
     new_r<-allocation_calculation(treatment_differences)
     interim_allocation_2<-rbind(interim_allocation_2,new_r)
     df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
     interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_post
                                      beta_prior = aux_post$alpha_beta_params$beta_poster
                                      eta=0.95, zeta=0.90,xi=0.95,
                                      r=new_r,
                                      q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                      delta_star=0.3)
     interim_ss_rar_2<-rbind(interim_ss_rar_2,interim_aux)
  }
  colMeans(interim_ss_rar_2,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  38.39542   41.39656   64.08651   76.97894
```

Hypothetical Scenario #10

Treatment effects 0, 0.1, 0.2, 0.6, clinically relevant difference is 0.2. One interim analysis at 25% recruited another at 75% recruited

```
alpha<-1:10000
beta<-alpha
df_sample_size<-tibble()
df_posteriors<-tibble()
df_q_andmu_posteriors<-tibble()
df_alpha_beta_posteriors<-tibble()
df_D_posteriors<-tibble()
interim_allocation_1<-tibble()
interim_ss_rar_1<-tibble()
interim_allocation_2<-tibble()
interim_ss_rar_2<-tibble()
for(i in 1:1000){
  alpha1<-sample(alpha,1)
  beta1<-beta[alpha1==alpha]
  aux<-sample_size_calculation(alpha_prior = alpha1,beta_prior = beta1,
                               eta=0.95, zeta=0.90,
                               xi=0.95,r=c(1/4,1/4,1/4,1/4),
                               q_prior=c(2,2,2,2),delta_star=0.2)
  if(any(is.na(aux)))next
  y1_aux=rnorm(round(aux$treatment1/4),mean=0, sd=1)
  y2_aux=rnorm(round(aux$treatment2/4),mean=0.1, sd=1)
  y3_aux=rnorm(round(aux$treatment3/4),mean=0.2, sd=1)
  y4_aux=rnorm(round(aux$treatment4/4),mean=0.6, sd=1)

  y=c(y1_aux,y2_aux,y3_aux,y4_aux)
  treatment_assignment<-c(rep(1,round(aux$treatment1/4)),
                          rep(2,round(aux$treatment2/4)),
                          rep(3,round(aux$treatment3/4)),
                          rep(4,round(aux$treatment4/4)))
  df=tibble(treatment_assignment,y)
  aux_post<-posterior_calculations(alpha_prior=alpha1,beta_prior=beta1,
                                   q_prior=c(2,2,2,2),mu_prior=c(0,0,0,0),
                                   N_treat = c(round(aux$treatment1/4),
                                               round(aux$treatment2/4),
                                               round(aux$treatment3/4),
                                               round(aux$treatment4/4)),
```

```
                                                y_treatment = df)
treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                aux_post$D,
                                                aux_post$alpha_beta_params)
new_r<-allocation_calculation(treatment_differences)
interim_allocation_1<-rbind(interim_allocation_1,new_r)
df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_poste
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                     eta=0.95, zeta=0.90,xi=0.95,
                                     r=new_r,
                                     q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                     delta_star=0.2)
interim_ss_rar_1<-rbind(interim_ss_rar_1,interim_aux)
if(any(is.na(interim_aux)))next
y1_aux=rnorm(max(round((interim_aux$treatment1*0.75-aux$treatment1/4)),1),mean=0, sd=1)
y2_aux=rnorm(max(round((interim_aux$treatment2*0.75-aux$treatment2/4)),1),mean=0.1, sd=1
y3_aux=rnorm(max(round((interim_aux$treatment3*0.75-aux$treatment3/4)),1),mean=0.2, sd=1
y4_aux=rnorm(max(round((interim_aux$treatment4*0.75-aux$treatment4/4)),1),mean=0.6, sd=1
y_aux=c(y1_aux,y2_aux,y3_aux,y4_aux)
treatment_assignment<-c(rep(1,max(round((interim_aux$treatment1*0.75-aux$treatment1/4)),
                        rep(2,max(round((interim_aux$treatment2*0.75-aux$treatment2/4)),
                        rep(3,max(round((interim_aux$treatment3*0.75-aux$treatment3/4)),
                        rep(4,max(round((interim_aux$treatment4*0.75-aux$treatment4/4)),
 df_aux=tibble(treatment_assignment,y=y_aux)
 df<-rbind(df,df_aux)
 df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
 aux_post<-posterior_calculations(alpha_prior =aux_post$alpha_beta_params$alpha_posterio
                                     beta_prior = aux_post$alpha_beta_params$beta_poster
                                  q_prior =as.numeric( df_q_andmu_posteriors[,grep("q",co
                                  mu_prior= as.numeric( df_q_andmu_posteriors[,grep("mu",
                                  N_treat = c(round(interim_aux$treatment1*0.75),
                                              round(interim_aux$treatment2*0.75),
                                              round(interim_aux$treatment3*0.75),
                                              round(interim_aux$treatment4*0.75)),
                                              y_treatment = df)
  treatment_differences<-get_treatment_difference(aux_post$q_andmu_posteriors,
                                                aux_post$D,
                                                aux_post$alpha_beta_params)
 new_r<-allocation_calculation(treatment_differences)
 interim_allocation_2<-rbind(interim_allocation_2,new_r)
```

```
    df_q_andmu_posteriors<-aux_post$q_andmu_posteriors
    interim_aux<-sample_size_calculation(alpha_prior =aux_post$alpha_beta_params$alpha_post
                                         beta_prior = aux_post$alpha_beta_params$beta_poster
                                         eta=0.95, zeta=0.90,xi=0.95,
                                         r=new_r,
                                         q_prior =as.numeric( df_q_andmu_posteriors[,grep("q
                                         delta_star=0.2)
    interim_ss_rar_2<-rbind(interim_ss_rar_2,interim_aux)
  }
  colMeans(interim_ss_rar_2,na.rm = T)
```

```
treatment1 treatment2 treatment3 treatment4
  74.05812   97.57450  140.02494  148.01546
```