Randomization and sample size estimation

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2023-12-27

Contents

Introduction:

The aim of this demo is to showcase how to estimate sample sizes and conduct randomization in clinical trial designs. R has a suite of packages geared towards clinical trial design, monitoring, and analyses (CRAN R Projects- Clinical Trials Zhang, Zhang, and Zhang (2021)). I'm also modeling my demo off of Peter Higgin's *Reproducible Medical Research with R* book, chapter 20 (Higgins (2023)).

Load Libraries

```r
library(tidyverse) # for ggplot2, data visualization and data filtering with dplyr
library(ggbeeswarm) # for quasirandom plotting
library(pwr) # power analysis
library(gsDesign) # power analysis for survival
library(blockrand) # randomization package

#ggplot2 settings I like:
T<-theme_bw()+theme(,text=element_text(size=18),
                    axis.text=element_text(size=18),
                    panel.grid.major=element_blank(),
                    panel.grid.minor.x = element_blank(),
                    panel.grid = element_blank(),
                    legend.key = element_blank(),
                    axis.title.y=element_text(margin=margin(t=0,r=15,b=0,l=0)),
                    axis.title.x=element_text(margin=margin(t=15,r=,b=0,l=0)))
#+ theme(legend.position="none")
```

Sample size calculations

It is important to find the appropriate number of participants in a clinical trial because too few participants may lead to an inability to detect differences (studies may be underpowered) and too many participants lead to excessive use of resources.

The critical information to obtain are:

- alpha (α) level - probability of committing a type I error (false positive)

- beta (β) level - probability of committing a type II error (false negative)
    - sometimes the program will ask for power, which is 1-β and is the probability of detecting differences if they truly exist

- effect size between groups (*cohen's d*)
    - Note that cohen's d is expressed as: $\frac{(\bar{\mu}_1 - \bar{\mu}_2)}{S_{pooled}}$, where $\bar{\mu}_1$ is the mean of one group and $\bar{\mu}_2$ is the mean of the other group, and S_{pooled} is the pooled standard deviation. Therefore, cohen's d is interpreted in units of standard deviation.

- drop out rates

Other information to consider for survival analyses:

- rate of enrollment

- length of study

- hazard rate of each group

T-test designs and sample size calculations

We will be using the *pwr* package. To start, let's estimate a sample size with:

- alpha = 0.05

- power = 0.80 (1-β)

- effect size, cohen's d = 0.5, which is considered a moderate effect size

```
pwr::pwr.t.test(sig.level=0.05,type="two.sample",power=.8,d=.5)
```

```
##
##      Two-sample t test power calculation
##
##              n = 63.76561
##              d = 0.5
##       sig.level = 0.05
##          power = 0.8
##     alternative = two.sided
##
## NOTE: n is number in *each* group
```

Key result: 64 volunteers per arm. We round up because there can be no fractional individuals.

For a different study design, let's assume there is a before and after measurement of a continuous variable and this would produce paired results with the same assumptions about α,β, and cohen's d.

```
pwr::pwr.t.test(sig.level=0.05,type="paired",power=.8,d=.5)
```

```
##
##      Paired t test power calculation
##
##              n = 33.36713
##              d = 0.5
##       sig.level = 0.05
##          power = 0.8
##     alternative = two.sided
##
## NOTE: n is number of *pairs*
```

Key result: 34 volunteers per arm.

We also may need to consider drop out rates. For example, if there is a 20% drop out rate, then add 20% to the sample sizes per arm. 34 x 20% = ~7, so we would need 41 volunteers.

Simulating effect sizes and power

What if we don't know the effect size and want to find out sample sizes based on different inputs of effect size and power?

- simulating effect sizes from 0 to 2 in .1 increments

- over two levels of power (0.8 and .9)

```r
#code to get sample size from pwr.t.test
#round(pwr::pwr.t.test(sig.level=0.05,type="two.sample",power=.8,d=c(.5),n=NULL)$n,0)

d<-data.frame(efsize=rep(seq(0.1,2,.1),2),
              power=c(rep(.8,length(seq(0.1,2,.1))),
                      rep(.9,length(seq(0.1,2,.1)))))
d%>%
  group_by(efsize,power)%>%
  mutate(n=round(pwr::pwr.t.test(sig.level=0.05,
                                 type="two.sample",power=power,
                                 d=efsize,n=NULL)$n,0),
         power2=paste("Power = ",power,sep=""))%>%
  #power2 is for plotting
  ggplot(.,aes(x=efsize,y=n,colour=factor(power)))+
  geom_point()+geom_line()+
  theme_minimal()+
  geom_text(aes(label=n),vjust=-1)+
  facet_wrap(~power2,ncol=1)+
  xlab("Effect size (cohen's d)")+
  ylab("Sample size per arm")+
  theme(legend.position = "none")+
  scale_x_continuous(,limits=c(0,2)
                     ,breaks=seq(0,2,.25),
                     labels=seq(0,2,.25))+
  scale_y_continuous(limits=c(0,2500))
```
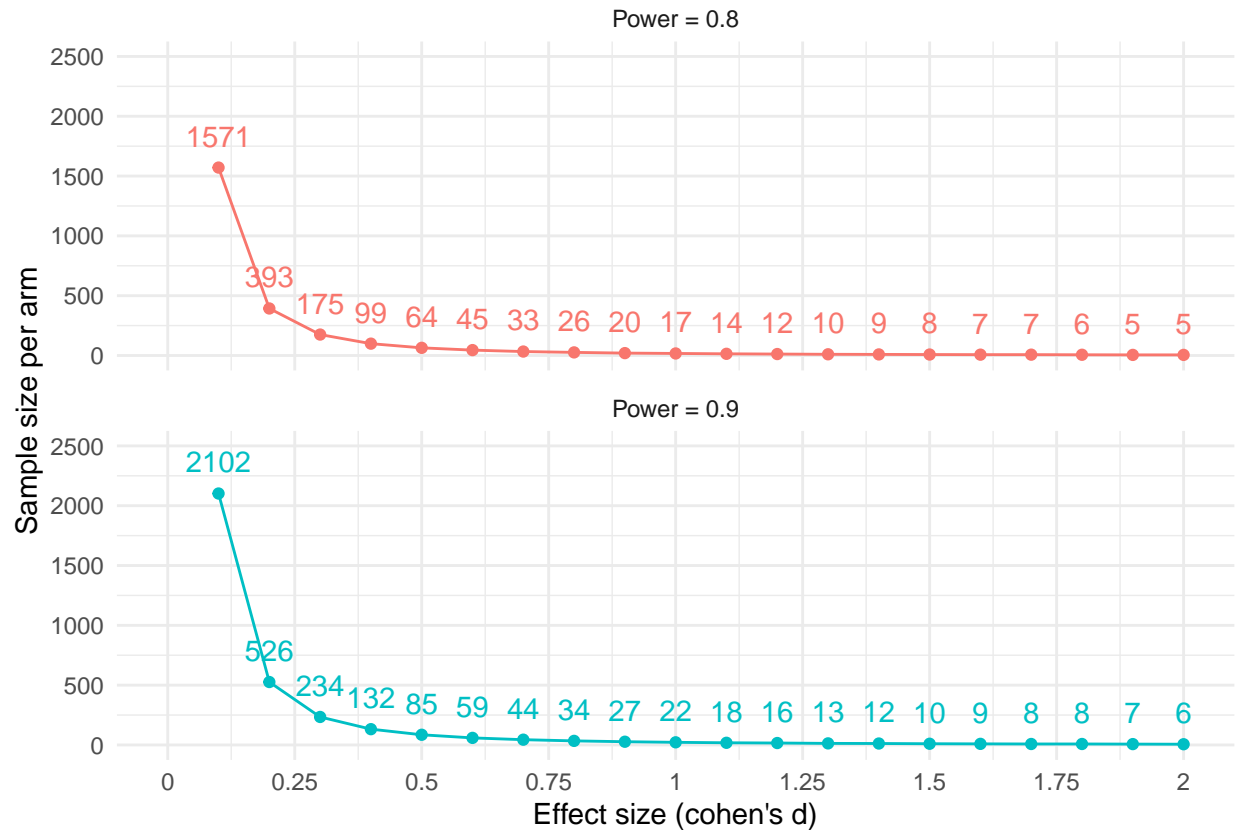
Chi-square 2x2 contingency table design

In this design, let's say there are counts of diseased and not-diseased individuals that were exposed and not exposed to some chemical. We want to find the association between the two variables and we need to specify the expected proportions of the 2x2 under the alternative hypothesis.

```r
#ES.w2() # chi-square for test of association
#pwr.chisq.test()

d2<-data.frame(exposure=c("exposed","not exposed"),non_diseased=c(.25,.3),diseased=c(0.25,.2))
knitr::kable(d2)
```

exposure	non_diseased	diseased
exposed	0.25	0.25
not exposed	0.30	0.20

Now that we have the expected 2x2 matrix under the alternative hypothesis (not independent), then we need to identify the effect size with *ES.w2()* and then plug and chug with *pwr.chisq.test()* with $\alpha = 0.05$ and power $= 0.8$.

```r
ef.sim.dat<-ES.w2(d2[,-1])
pwr.chisq.test(w=ef.sim.dat,df=1,power=.8,sig.level=.05)
```

```
##
##      Chi squared power calculation
##
##              w = 0.1005038
##              N = 777.0372
##             df = 1
##      sig.level = 0.05
##          power = 0.8
##
## NOTE: N is the number of observations
```

Key result: We need 778 observations. Note that the degrees of freedom on 1 in this case for a 2x2 contingency table, which is calculated as (# of columns - 1) x (# of rows -1).

Time to event types of designs (survival analyses)

I will be using the *gsDesign* package and referencing an online resource **here**.

```
hr=.7 # hazard ratio
controlMedian<-8 # 8 months
lambda1 <- log(2) / controlMedian #estimated hazard rate of control

nSurvival(
  lambda1 = lambda1,
  lambda2 = lambda1 * hr, #hazard rate for experimental
  Ts = 24, #24 months
  Tr = 6, # 6 months
  eta = .1, # value per month dropout rate
  ratio = 1, # equal sampling
  alpha = .05,
  beta = .2
)
```

```
## Fixed design, two-arm trial with time-to-event
## outcome (Lachin and Foulkes, 1986).
## Study duration (fixed):          Ts=24
## Accrual duration (fixed):        Tr=6
## Uniform accrual:             entry="unif"
## Control median:      log(2)/lambda1=8
## Experimental median: log(2)/lambda2=11.4
## Censoring median:        log(2)/eta=6.9
## Control failure rate:       lambda1=0.087
## Experimental failure rate:  lambda2=0.061
## Censoring rate:              eta=0.1
## Power:                100*(1-beta)=80%
## Type I error (1-sided):   100*alpha=5%
## Equal randomization:         ratio=1
## Sample size based on hazard ratio=0.7 (type="rr")
## Sample size (computed):          n=476
## Events required (computed): nEvents=195
```

Randomization

Using the t-test design (2 trial arms), we'd like to implement block randomization across a strata. Often times, we can't sample participants all at once and so we need to apply treatments in groupings as they enroll in the study, or blocks. To ensure equal sampling of treatments across different sub-populations, randomization can be conducted at the level of different sub-populations (strata). For example, randomization can be conducted for males and females separately. With a sample size of 100 per arm, in a two-arm trial, I'm randomization across a gender strata.

```r
mrand<-blockrand(n = 100,
                 num.levels = 2, # three treatments
                 levels = c("Con.Arm", "Treat.Arm"), # arm names
                 stratum = "Strat.male", # stratum name
                 id.prefix = "SM", # stratum abbrev
                 block.sizes = c(3,4), # times arms = 6,8
                 block.prefix = "blksm") # stratum abbrev

frand<-blockrand(n = 100,
                 num.levels = 2, # three treatments
                 levels = c("Con.Arm", "Treat.Arm"), # arm names
                 stratum = "Strat.female", # stratum name
                 id.prefix = "SF", # stratum abbrev
                 block.sizes = c(3,4), # times arms = 6,8
                 block.prefix = "blkfm") # stratum abbrev
totrand<-rbind(mrand,frand)
knitr::kable(head(totrand,25))
```

id	stratum	block.id	block.size	treatment
SM001	Strat.male	blksm01	8	Treat.Arm
SM002	Strat.male	blksm01	8	Treat.Arm
SM003	Strat.male	blksm01	8	Treat.Arm
SM004	Strat.male	blksm01	8	Con.Arm
SM005	Strat.male	blksm01	8	Con.Arm
SM006	Strat.male	blksm01	8	Treat.Arm
SM007	Strat.male	blksm01	8	Con.Arm
SM008	Strat.male	blksm01	8	Con.Arm
SM009	Strat.male	blksm02	6	Con.Arm
SM010	Strat.male	blksm02	6	Con.Arm
SM011	Strat.male	blksm02	6	Con.Arm
SM012	Strat.male	blksm02	6	Treat.Arm
SM013	Strat.male	blksm02	6	Treat.Arm
SM014	Strat.male	blksm02	6	Treat.Arm
SM015	Strat.male	blksm03	6	Treat.Arm
SM016	Strat.male	blksm03	6	Treat.Arm
SM017	Strat.male	blksm03	6	Treat.Arm
SM018	Strat.male	blksm03	6	Con.Arm
SM019	Strat.male	blksm03	6	Con.Arm
SM020	Strat.male	blksm03	6	Con.Arm
SM021	Strat.male	blksm04	8	Con.Arm
SM022	Strat.male	blksm04	8	Treat.Arm
SM023	Strat.male	blksm04	8	Con.Arm
SM024	Strat.male	blksm04	8	Con.Arm

id	stratum	block.id	block.size	treatment
SM025	Strat.male	blksm04	8	Treat.Arm

We can then create patient randomization "cards" based on the *blockrand()* output.

```r
plotblockrand(totrand,'mystudy.pdf',
              top=list(text=c('MyStudy','Patient:%ID%','Treatment:%TREAT%'),
                       col=c('black','black','red'),font=c(1,1,4)),
              middle=list(text=c("MyStudy","Sex:%STRAT%","Patient:%ID%"),
                          col=c('black','blue','green'),font=c(1,2,3)),
              bottom="Call123-4567toreportpatiententry", cut.marks=TRUE)
```

Session Info

```r
sessionInfo()
```

```
## R version 4.3.2 (2023-10-31 ucrt)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 10 x64 (build 19045)
##
## Matrix products: default
##
##
## locale:
## [1] LC_COLLATE=English_United States.utf8
## [2] LC_CTYPE=English_United States.utf8
## [3] LC_MONETARY=English_United States.utf8
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United States.utf8
##
## time zone: America/New_York
## tzcode source: internal
##
## attached base packages:
## [1] stats     graphics  grDevices utils     datasets  methods   base
##
## other attached packages:
##  [1] blockrand_1.5   gsDesign_3.6.0   pwr_1.3-0        ggbeeswarm_0.7.2
##  [5] lubridate_1.9.2 forcats_1.0.0   stringr_1.5.0    dplyr_1.1.2
##  [9] purrr_1.0.2     readr_2.1.4     tidyr_1.3.0      tibble_3.2.1
## [13] ggplot2_3.4.3   tidyverse_2.0.0
##
## loaded via a namespace (and not attached):
##  [1] gt_0.10.0        utf8_1.2.3       generics_0.1.3   xml2_1.3.5
##  [5] r2rtf_1.1.1      stringi_1.7.12   hms_1.1.3        digest_0.6.33
##  [9] magrittr_2.0.3   evaluate_0.21    grid_4.3.2       timechange_0.2.0
## [13] fastmap_1.1.1    fansi_1.0.4      scales_1.2.1     cli_3.6.1
## [17] rlang_1.1.1      munsell_0.5.0    withr_2.5.0      yaml_2.3.7
## [21] tools_4.3.2      tzdb_0.4.0       colorspace_2.1-0 vctrs_0.6.3
```

```
## [25] R6_2.5.1          lifecycle_1.0.3   vipor_0.4.5       pkgconfig_2.0.3
## [29] beeswarm_0.4.0    pillar_1.9.0      gtable_0.3.4      glue_1.6.2
## [33] highr_0.10        xfun_0.40         tidyselect_1.2.0  rstudioapi_0.15.0
## [37] knitr_1.43        farver_2.1.1      xtable_1.8-4      htmltools_0.5.6
## [41] labeling_0.4.2    rmarkdown_2.24    compiler_4.3.2
```

References

Higgins, Peter D. R. 2023. *Chapter 20 Randomization for Clinical Trials with R | Reproducible Medical Research with R*. https://bookdown.org/pdr_higgins/rmrwr/randomization-for-clinical-trials-with-r.html.

Zhang, Ed, W. G. Zhang, and R. G. Zhang. 2021. "CRAN Task View: Clinical Trial Design, Monitoring, and Analysis." https://CRAN.R-project.org/view=ClinicalTrials.