UCDAVIS HEALTH

Topics in Designing Phase III Clinical Trials

CLINICAL AND TRANSLATIONAL SCIENCE CENTER

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Learning objectives

- Understand the objectives and interpretation of **superiority**, **equivalence**, and **non-inferiority** trials
- Know how to approach sample size estimation for **equivalence** and **non-inferiority** trials
- Appreciate the appropriate use of **interim** analyses and stopping rules in clinical trials

Clinical trials classification

- Active control trials: test drug is concurrently compared to an known active drug.
- Possible primary objectives
  - To demonstrate **superiority** of the test drug over the active control
  - To show that the test drug is similar to the active control: **equivalence** trial
  - To verify that the test drug is no worse than the active control: **non-inferiority** trial

Superiority trials

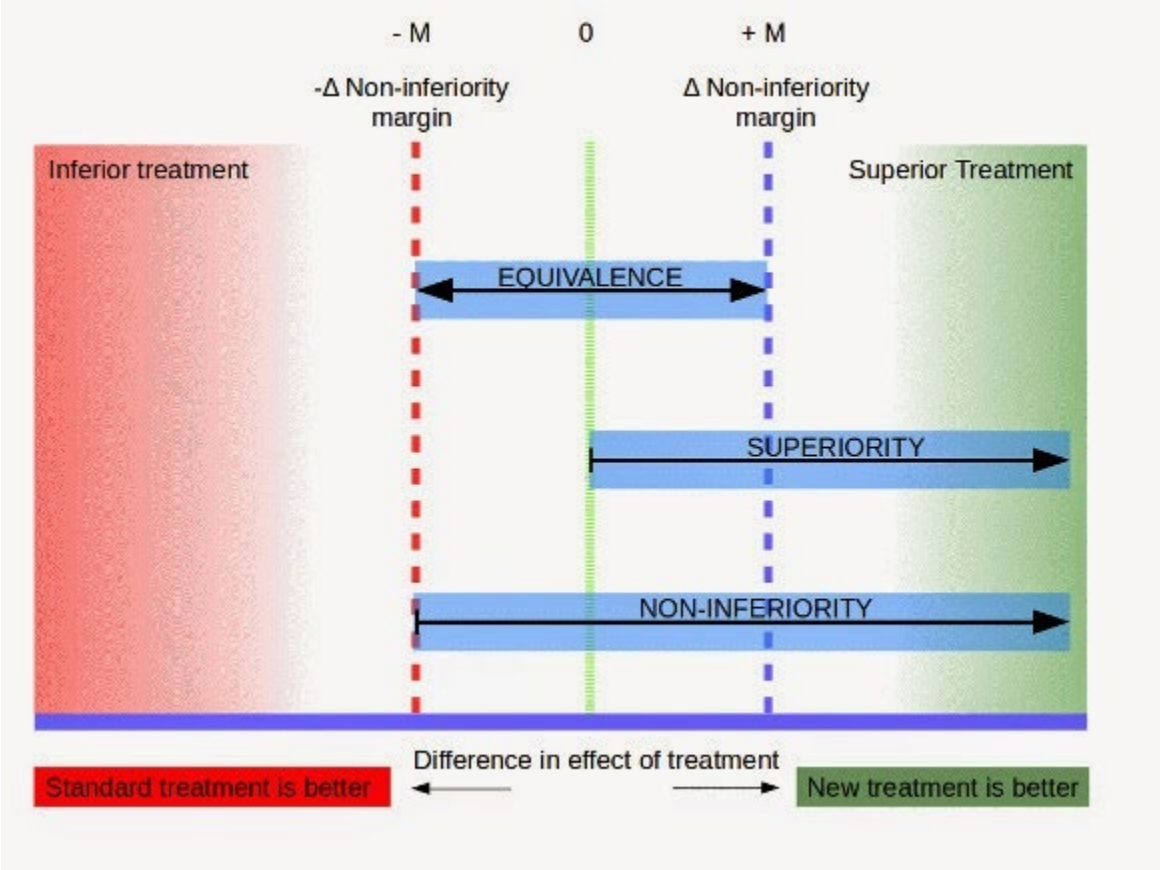
- Primary objective (Chow & Liu): showing that the investigational agent is superior to the comparative agent
  - First, prove that there is a statistically significant difference between the effects of the agents
  - Then show that the difference is in the correct direction

Design and Analysis of Clinical Trials (3rd Ed.)
Chow & Liu, Wiley, 2014

Superiority trials

- The **null hypothesis** (H_0) assumes that there is no difference in outcome between the two groups.
- The **alternative hypothesis** (H_A) assumes that one group has a more favorable outcome than the other.
- The **research hypothesis** is usually the alternative hypothesis.

Clinical Trials Classification



http://www.pvanuden.com/2015/04/equivalence-vs-non-inferiority-vs.html

Superiority trial: hypotheses

- μ_I = intervention group mean
- μ_C = control group mean
- H_0: $\mu_I = \mu_C$
- H_A: $\mu_I \neq \mu_C$
- Reject H_0 if the (1-α) 2-sided confidence interval for $\mu_I - \mu_C$ does not include zero.

Test statistic to compare means: two independent samples

$$z = \frac{\bar{x} - \bar{y}}{\sigma\sqrt{2/n}}$$

- $\bar{x}$ = intervention group mean
- $\bar{y}$ = control group mean
- σ^2 = common variance in each group
- n = sample size in each group

Wittes, Epidemiol Rev, 2002; 24(1):39-53 (eq. 1)

Equivalence and non-inferiority trials

- Equivalence
  - Null hypothesis: effects of the treatments are substantively different
  - Alternative hypothesis: difference between the treatment effects is within the equivalence limits
- Non-inferiority
  - Null hypothesis: the new treatment is substantively less effective than the control
  - Alternative hypothesis: the new treatment is not substantively worse than the control

Requirements

- The control must be demonstrably better than placebo or no treatment
  - Used with dose & formulation proven effective
  - Established for the indication being studied
  - Studies demonstrating benefit should be recent
  - Evidence of benefit must be available to estimate event rate in control group
- Response variable must be sensitive to postulated effects of control and intervention
  - Assay sensitivity: ability to show a difference if one exists

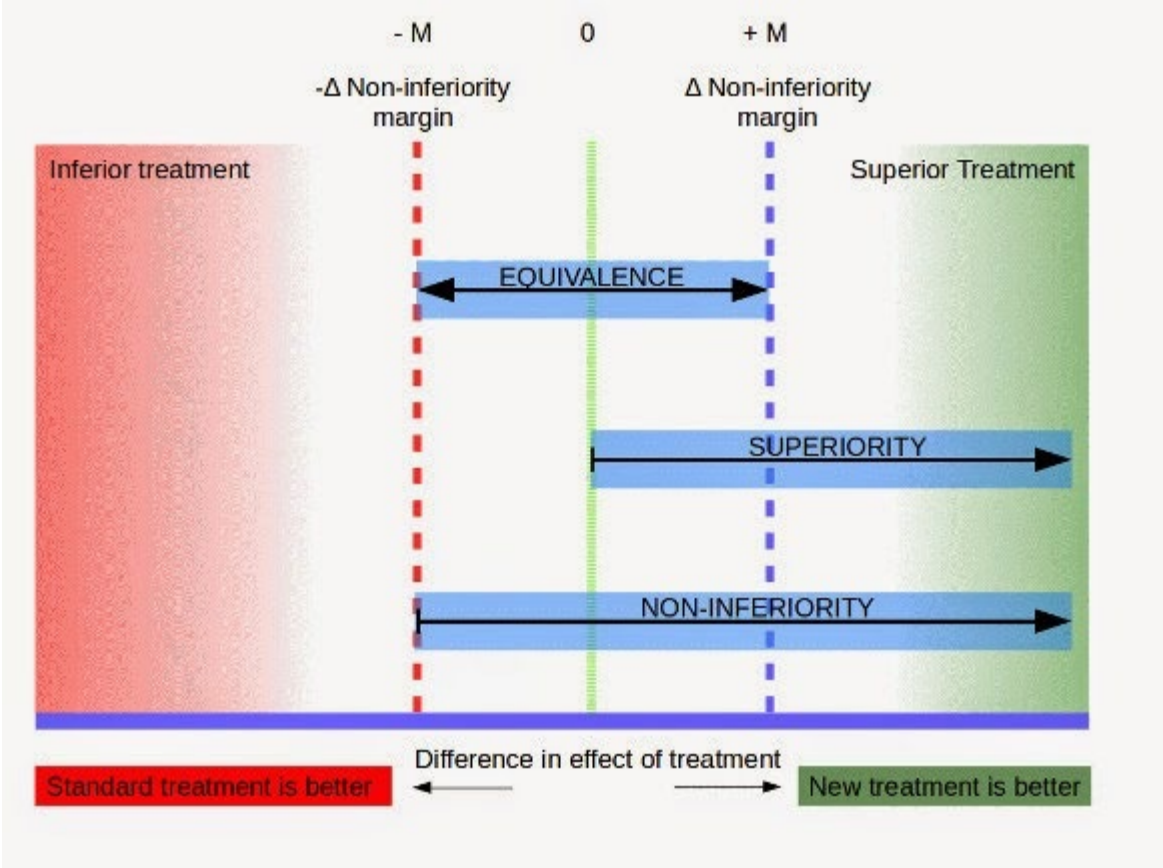
Equivalence limits

- Need to decide how close the effect of the new treatment must be to the control in order to be considered equivalent
  - Or how much smaller the effect can be and still be considered non-inferior
- Can be controversial

Equivalence trials

- The **null hypothesis** (H_0) assumes that the intervention group has an different outcome than the control group.
- The **alternative hypothesis** (H_A) assumes that the outcome of the intervention group is the same as that of the control group, within the **equivalence interval**.

Clinical Trials Classification



http://www.pvanuden.com/2015/04/equivalence-vs-non-inferiority-vs.html

Equivalence trial: hypotheses

- μ_I = intervention group mean
- μ_C = control group mean
- δ_1, δ_2 = equivalence limits
- H_0: $\mu_I - \mu_C \leq \delta_1$ or $\mu_I - \mu_C \geq \delta_2$
- H_A: $\delta_1 < \mu_I - \mu_C < \delta_2$
- Reject H_0 if the (1-2α) 2-sided confidence interval for $\mu_I - \mu_C$ is entirely within the interval $[\delta_1, \delta_2]$

Two one-sided tests (TOST) method

- H_{01}: $\mu_I - \mu_C \leq \delta_1$
- H_{A1}: $\mu_I - \mu_C > \delta_1$

- H_{02}: $\mu_I - \mu_C \geq \delta_2$
- H_{A2}: $\mu_I - \mu_C < \delta_2$

- If both H_{01} and H_{02} are rejected at level α (1-sided), the two treatments are considered equivalent.

Schuirmann, J Pharmocokin Biopharm15:657-680

Example: lymphedema trial

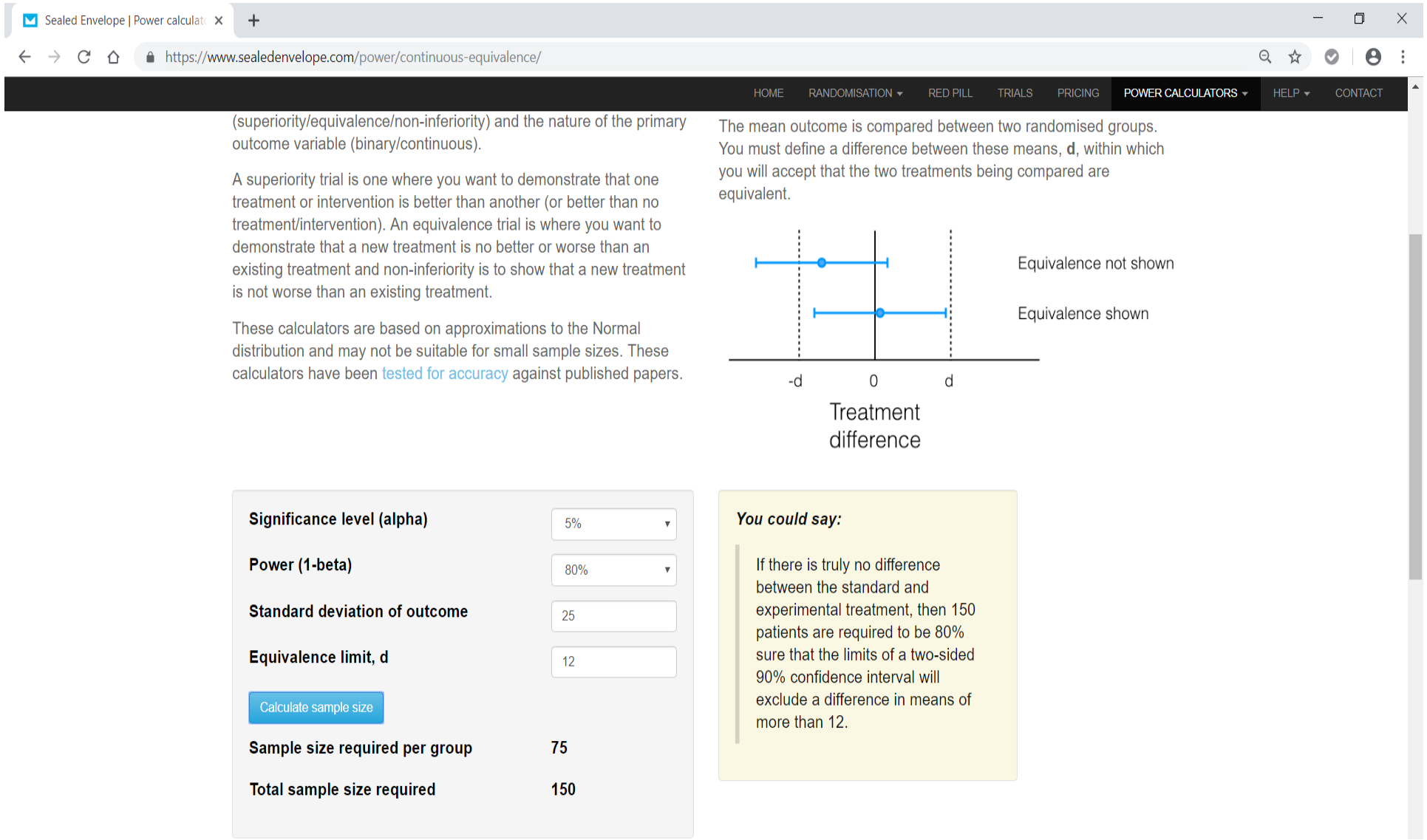
- Randomized, single-blind, equivalence trial testing whether physical therapy is equally effective in treatment of arm lymphedema in breast cancer patients if it includes manual lymphatic drainage or not.
- 4 weeks of treatment with 6-month follow-up
- Primary outcome: percentage volume reduction of arm lymphedema from baseline to 7 months
- Data analysis: ANCOVA with baseline value as covariate

Tambour et al., BMC Cancer 2014; 14:239

Lymphedema trial: assumptions for TOST sample size calculation

- **Level:** 5% (2-sided), or 5% for each 1-sided test
- **Power:** 80%
- **Outcome measure:** % change in lymphedema
- **Equivalence interval:** -12% to +12%
  - "Based on clinically and statistically important differences as well ethical criteria, cost, and feasibility"
- **True mean difference:** 0
- **Standard deviation:** 25%
  - No reason given for this SD
- n=76 patients per study arm=152 total
- Actual planned sample size=160 total

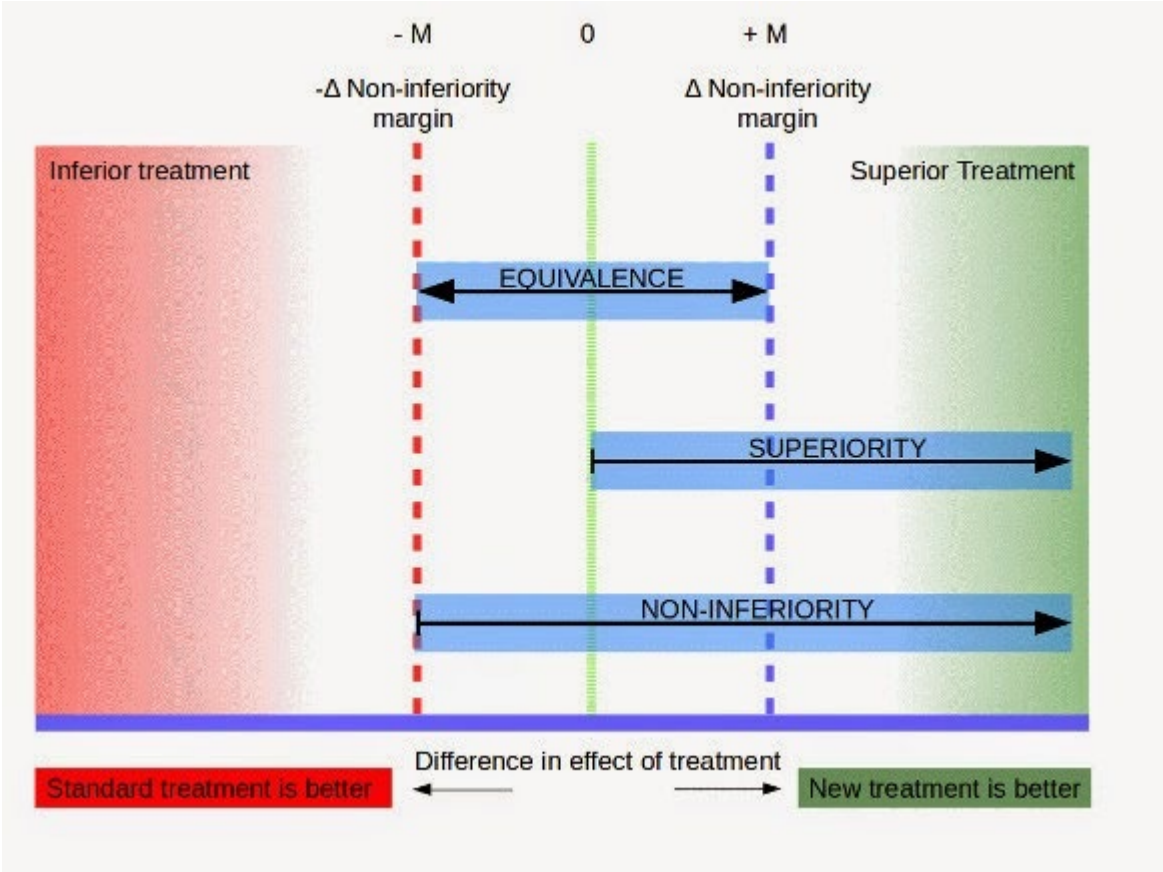
SealedEnvelope.com Equivalence Power Calculation



Non-inferiority trials

- The **null hypothesis** (H_0) assumes that the intervention group has an inferior outcome to the control group.
- The **alternative hypothesis** (H_A) assumes that the outcome of the intervention group is not inferior to that of the control group, within a certain margin.
  - Called the **margin of indifference** or margin of non-inferiority.

Clinical Trials Classification



http://www.pvanuden.com/2015/04/equivalence-vs-non-inferiority-vs.html

Non-inferiority trial: hypotheses

- μ_I = intervention group mean
- μ_C = control group mean
- δ = non-inferiority margin
- H_0: $\mu_I \leq \mu_C - \delta$
- H_A: $\mu_I > \mu_C - \delta$
- Reject H_0 if the (1-α) 2-sided confidence interval for $\mu_I - \mu_C$ is entirely above $-\delta$

Test statistic for non-inferiority trial

$$z = \frac{\bar{x} - \bar{y} - (-\delta)}{\sigma\sqrt{2/n}}$$

- $\bar{x}$ = intervention group mean
- $\bar{y}$ = control group mean
- σ^2 = common variance in each group
- n = sample size in each group
- δ = non-inferiority margin

Non-inferiority trial

- For a continuous variable, the sample size is the same as for a superiority trial, where the detectable difference is the same as the margin of non-inferiority.

Example: Genetic counseling for breast cancer patients

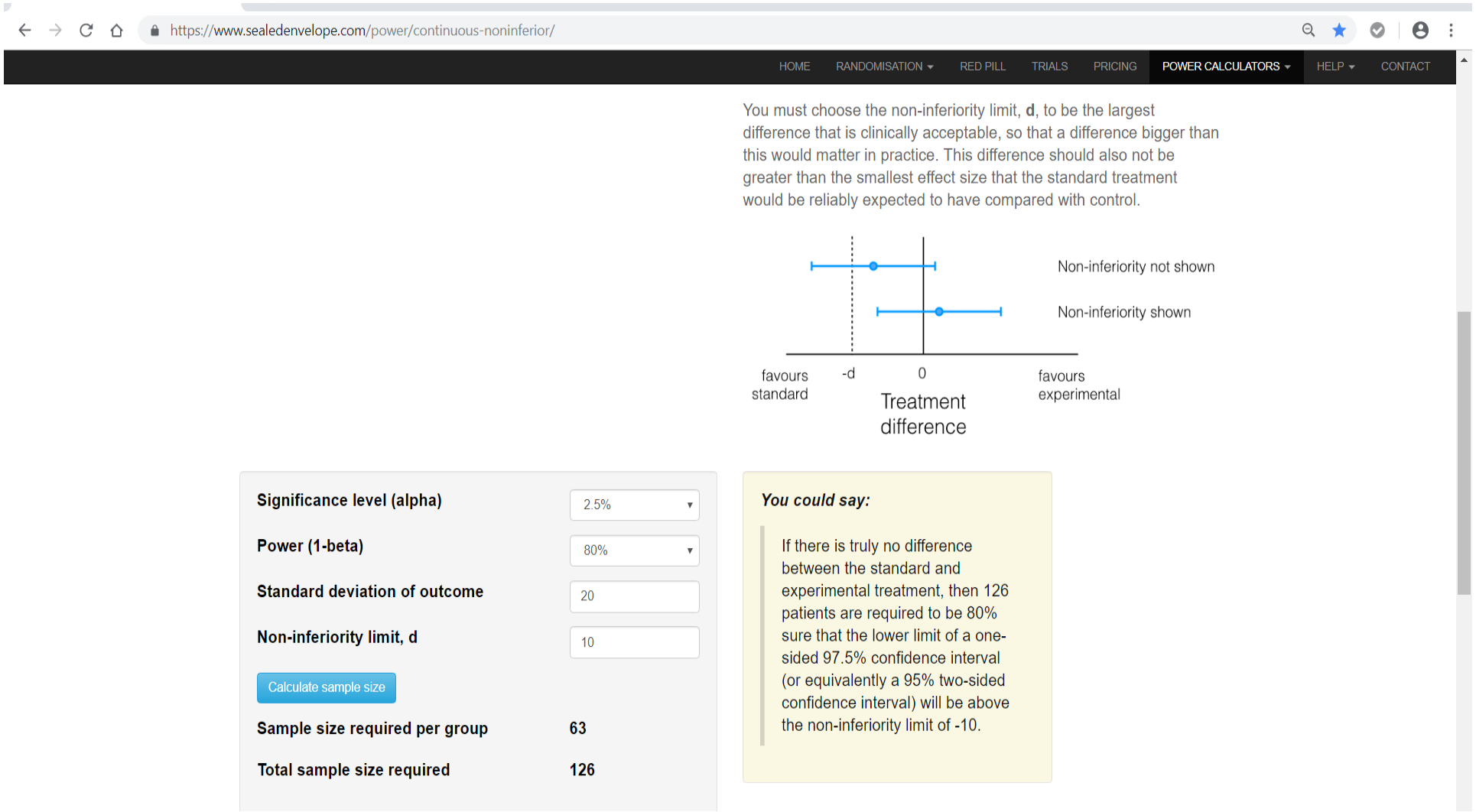
- Randomized non-inferiority trial testing the effect of a brochure vs. in-person counseling about treatment-focused genetic testing on various psycho-social variables and uptake of testing
- Primary outcome: decisional conflict
- Data analysis: linear regression for each outcome measured at 12 months, adjusting for baseline scores

Watts et al., BMC Cancer 2012; 12:320

Genetic counseling: assumptions for sample size calculation

- **Level:** 5% (2-sided)
- **Power:** 80%
- **Outcome measure:** Decisional Conflict Scale
- **Non-inferiority margin:** -10 units
  - Should be +10 units because higher values are bad
  - Corresponds to only 1 of 10 items answered “no”
- **True mean difference:** 0
- **Standard deviation:** 20
  - Deemed “conservative”
- n=64 patients per study arm=128 total
- Actual planned sample size=140 total

SealedEnvelope.com Non-inferiority Power Calculation



Decision for early termination

- Major valid reasons for early termination
  - Serious adverse effects in intervention group
  - Greater than expected beneficial effects
  - Statistically significant difference by the end of the study is unlikely (futility)
  - Problems conducting the study are severe and cannot be corrected
    - Logistical or data quality problems
    - Participant recruitment far behind
  - Question posed by the trial is no longer important

Interim analysis

- Definition: the statistical analysis of results while they are still accumulating

Ludbrook, BMC Medical Research Methodology 2003; 3:15.

Repeated testing for significance

- Monitoring response variables may involve repeated significance testing of accumulating data
- Problem: if the null hypothesis is true and multiple tests are made at the same level of significance alpha, the overall probability of rejecting the null hypothesis > alpha
  - The probability of Type I error will be too high

Adaptive designs

- Purpose (Chow): to give the investigator the flexibility to identify signals or trends of the test treatment without undermining the validity and integrity of the study
- Attractive features
  - Reflects real world medical practice
  - Ethical with respect to safety and efficacy
  - Flexible and efficient
- Concerns
  - Is the p-value or confidence interval correct?
  - Does the trial still answer the original question?

Group sequential methods

- Developed to address the problem of repeated testing
- Assign a critical value (boundary) for the test statistic at each interim analysis
- Ad hoc methods
  - Use a critical value of z=2.6 for interim and final analyses
  - Haybittle-Peto: Use a large critical value, say z=3.0, for interim analyses and use the usual critical value (1.96) at the final analysis
  - Problem: Type I error level is not guaranteed

Calendar time and information time

- Information time is the proportion of the maximum information that has been obtained at a given point in calendar time.
  - Maximum information is obtained when all participants have completed the study.
- At time t, information time is:
  - Time-to-event study: (number of events at time t) / (expected total number of events)
  - Otherwise (generally): (number of participants who have completed the study by time t) / (total planned number of participants)

Group sequential methods

- Assume that interim analyses are conducted at equal information times 1/K, 2/K, etc., for K tests
- Pocock
  - Uses the same critical value for each analysis
  - Critical value is determined so that the probability of Type I error = α if all K tests are performed
- O'Brien-Fleming
  - Uses larger critical values for earlier analyses
  - Critical value =$Z*\sqrt{K/i}$ for the i^{th} analysis, where Z* is chosen so that the probability of Type I error = α if all K tests are performed

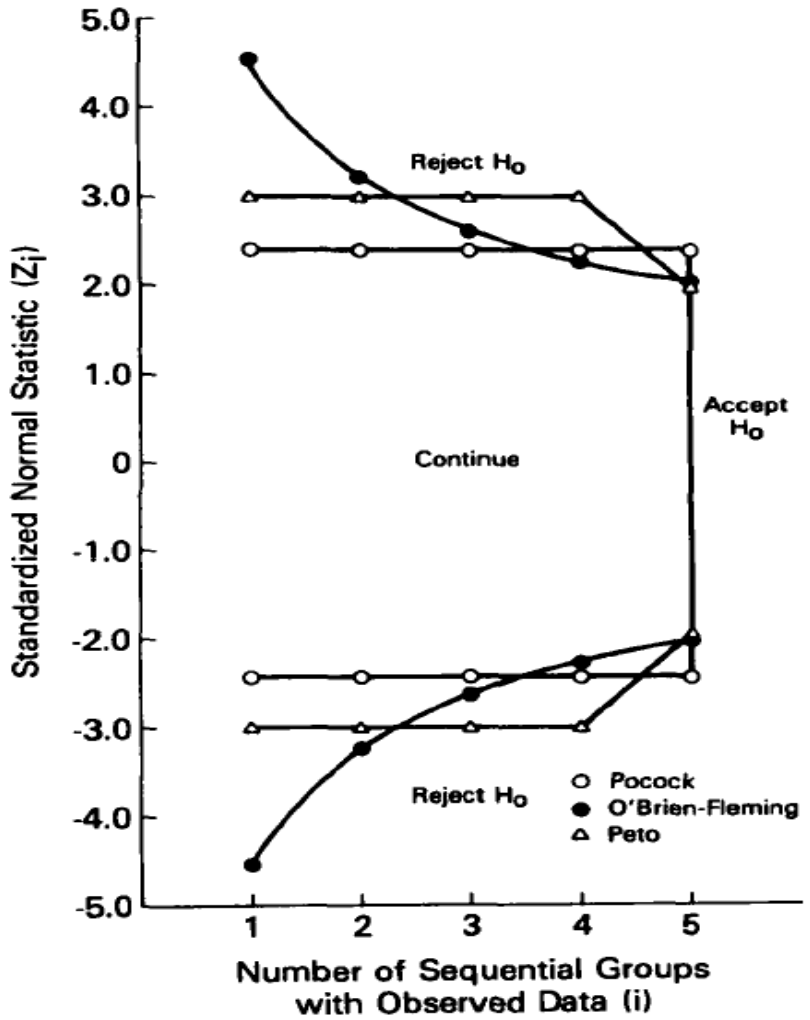


Figure 1. Two-sided 0·05 group sequential boundaries for Pocock, O'Brien–Fleming, and Peto–Haybittle methods for five planned analyses

Stat Med 1994; 13:1341-52

Flexible group sequential methods: spending functions

- Limitations of group sequential methods discussed so far
  - Need to specify number of interim analyses in advance
  - Interim analyses must be evenly spaced in information time
- However, it is possible to specify directly how much of alpha will be allocated to each interim analysis
- Advantage of alpha spending function: number and time of analyses need not be specified in advance
- Can also include beta spending function for futility

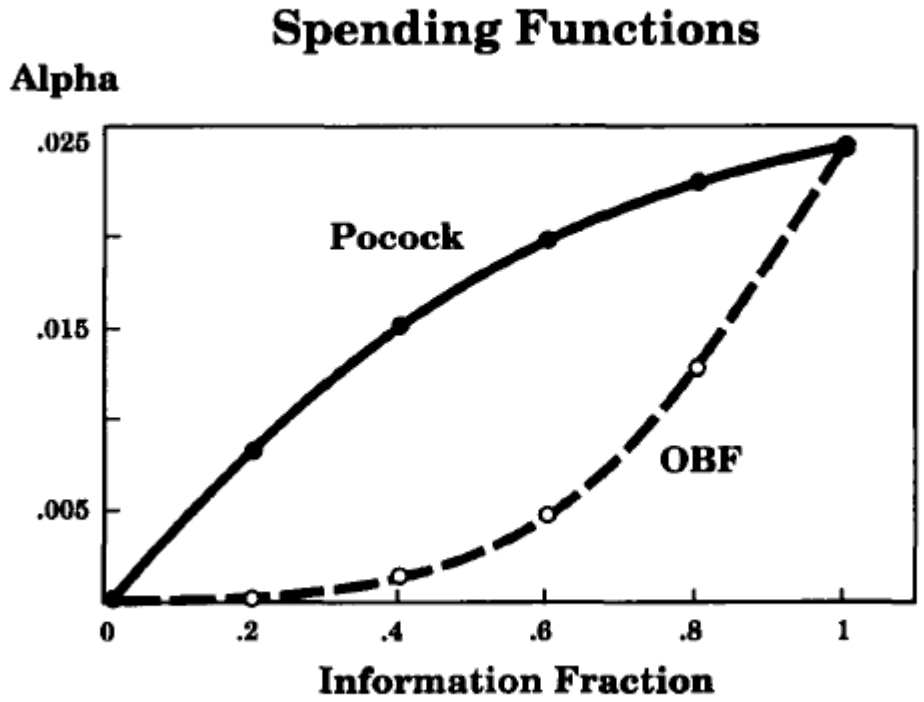


Figure 3. One-sided 0·025 alpha spending functions for Pocock and O'Brien–Fleming type boundaries

Stat Med 1994; 13:1341-52

Applications of group sequential boundaries

- Can be applied to any test statistic that:
  - Can be standardized with a normal distribution (turned into a z-value) and
  - Has independent increments of information between tests
- This includes comparisons of
  - Survival curves (log rank statistic)
  - Means
  - Proportions
  - Slopes

Asymmetric boundaries

- For a superiority trial, the interim analysis boundaries in the direction of benefit may be extreme
  - The benefit must be really, really great to stop the trial early
- However, the boundaries in the direction of harm may be less extreme
  - May not need evidence that harm is really, really great in order to stop the trial early

Sequential Design and Analysis with SAS

- At each stage, run the Use PROC SEQDESIGN to determine boundaries for rejecting and/or accepting the null hypothesis at each stage
- Analysis and use PROC SEQTEST to determine whether to continue to the next stage
- Reference: https://support.sas.com/resources/papers/proceedings09/311-2009.pdf

Example: Genetic Counseling

- Test of intervention to promote genetic counseling among low-income women at high risk for familial breast cancer
  - PI: Rena Pasick (UCSF); R01 CA129096
  - Original sample size: n=144 total—designed to detect 30% vs. 10% uptake of genetic counseling
  - Interim analysis planned with ADDPLAN 6 (Aptiv Solutions, Weston VA) conducted at n=72
  - Interim intervention effect: 35% vs. 5% ($p<0.001$, 1-sided).
  - Trial stopped for efficacy at n=88

Am J Public Health 2016; 106(10):1842-1848

```
ods graphics on;
*Plot of reject/accept boundaries with horizontal axis=sample size;
proc seqdesign
            plots=boundary(hscale=samplesize)
            ;
*1-sided O'Brien-Fleming Design with 2 stages;
*Stop to reject the null hypothesis;
  OneSidedOBrienFleming: design nstages=2
                  method(alpha)=obf
                                alpha=0.025
                                beta=0.20
                                alt=upper stop=reject
                  ;
*Test is comparison of proportions;
*Null proportion=0.1, alternative=0.3;
samplesize model=twosamplefreq(nullprop=0.1
            prop=0.3 test=prop);
*Output boundaries to use in testing;
ods output boundary=bound_prop;
run;
ods graphics off;
run;
```

One-Sided O'Brien-Fleming Design

- Stage 1
  - Enroll 30 participants in each group
  - Compute z-statistic for difference in proportions
  - If $z \geq 2.79651$, reject H_0 and stop
  - If $z < 2.79651$, continue to stage 2
- Stage 2
  - Enroll 30 participants in each group
  - Compute z-statistic for difference in proportions
  - If $z \geq 1.97743$, reject H_0 and stop
  - If $z < 1.97743$, accept H_0 and stop
- Sample size is ~1% larger than fixed sample size design

SAS Output

Boundary Information (Standardized Z Scale)
Null Reference = 0

Stage	Information Level Proportion	Information Level Actual	Information Level N	Alternative Reference Upper	Boundary Values Upper Alpha
1	0.5000	98.87478	59.32487	1.98872	2.79651
2	1.0000	197.7496	118.6497	2.81247	1.97743

Sample Size Summary

Test	Two-Sample Proportions
Null Proportion	0.1
Proportion (Group A)	0.3
Test Statistic	Z for Proportion

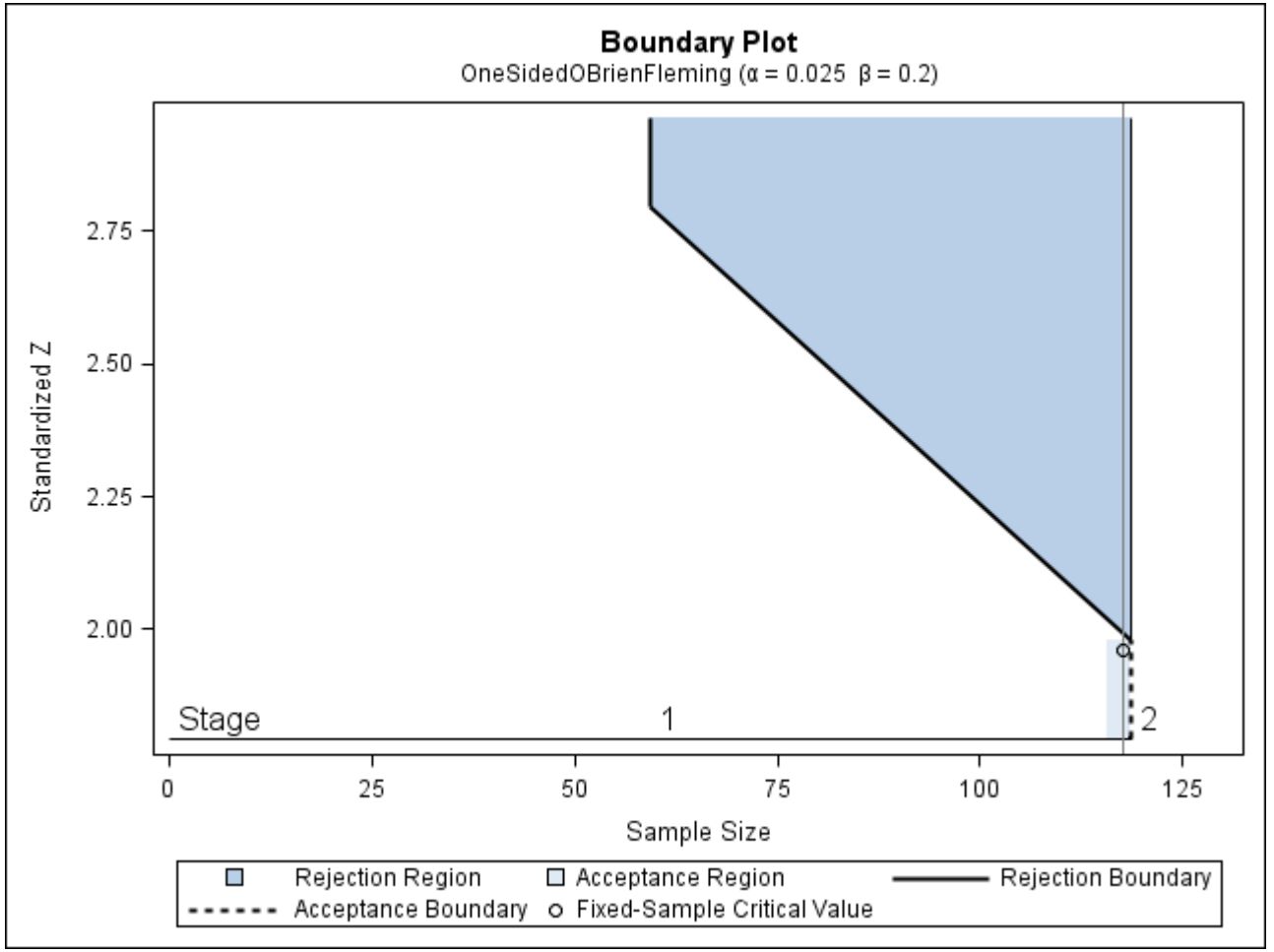
The SEQDESIGN Procedure
Design: OneSidedOBrienFleming

Sample Size Summary

Reference Proportions	Alt Ref
Max Sample Size	118.6497
Expected Sample Size (Null Ref)	118.4965
Expected Sample Size (Alt Ref)	106.2149

Sample Sizes (N)
Two-Sample Z Test for Proportion Difference

Stage	Fractional N	Fractional N(Grp 1)	Fractional N(Grp 2)	Fractional Information	Ceiling N	Ceiling N(Grp 1)	Ceiling N(Grp 2)	Ceiling Information
1	59.32	29.66	29.66	98.8748	60	30	30	100.0
2	118.65	59.32	59.32	197.7	120	60	60	200.0


Boundary Plot
OneSidedOBrienFleming (α = 0.025 β = 0.2)
Standardized Z
2.75
2.50
2.25
2.00
Stage
1
2
0
25
50
75
100
125
Sample Size
Rejection Region
Acceptance Region
Rejection Boundary
Acceptance Boundary
Fixed-Sample Critical Value