اندازه نمونه در مطالعات تحلیلی

Sample Size in Analytical Studies

Factors Determining Sample Size

- Number of **groups** and subgroups within the sample
- Value of **information** in the study
- **Accuracy** level required in results
- **Cost** of sample
- **Variability** of the population
- Sampling **Method**
- **…….**

Effect of sample size on estimation: a simulation

	True mean: 100 True σ: 15		True mean: 100 True σ : 35	
Sample size	Estimated M	SD	Estimated M	SD
10	98.0	11.0	108.9	32.2
50	100.4	13.6	95.3	41.4
100	101.3	14.4	99.1	35.5
200	99.9	15.2	100.3	33.2
500	99.8	15.3	98.9	33.8
1000	99.5	15.1	99.9	35.0
2000	99.7	15.0	99.9	34.7
10000	100.1	15.0	99.9	35.0
100000	100.0	15.0	100.0	35.0

Practical difference vs statistical significance

Outcome	Group A	Group B
Improved	9	18
No improved	21	12
Total	30	30
% improved	30%	60%

Chi-square: 5.4; P < 0.05
"Statistically significant"

Outcome	Group A	Group B
Improved	6	12
No improved	14	8
Total	20	20
% improved	30%	60%

Chi-square: 3.3; P > 0.05
"Statistically insignificant"

Underlying Statistical Principles in Hypothsis Testing

- Type one error
- Type two error, power
- Effect size

Effect Size

- Effect size is the size of the association(or difference) that an investigator would like to be able to detect or that would be clinically important.
- Smallest difference worth detecting.
- Selecting appropriate effect size is the most **difficult** aspect of sample size planning

How to find the effect size

- Prior studies
- Choose the smallest effect size that is clinically meaningful.
- Do a small pilot.

Reality / Test Result Statistical Analysis show that:	H_0 is really true **(Drug A and Drug B really have same effect)**	H_0 is really false **(Drug A and Drug B really have different effects)**
Accept H_0 **No difference is observed between Drug A and Drug B**		
Reject H_0 **Significant difference is observed between Drug A and Drug B**		

Reality / Test Result Statistical Analysis show that:	H_0 is really true **(Drug A and Drug B really have same effect)**	H_0 is really false **(Drug A and Drug B really have different effects)**
Accept H_0 **No difference is observed between Drug A and Drug B**		**Type II error** β
Reject H_0 **Significant difference is observed between Drug A and Drug B**	**Type I error** α	**Power** $1-\beta$

Type I Error

Type one Error (false-positive) : α

- Error in claiming a difference when there is none.
- Occur when an investigator rejects a null hypothesis that is actually true in the population (convict an innocent).

Type I Error

- α=0.05 means ….
  - the investigator has set 5% as the maximum chance of incorrectly rejecting the null hypothesis
- α=0.01 Need a very strong evidence to claim significance.
- α=0.1 With a little evidence the difference will be claimed.

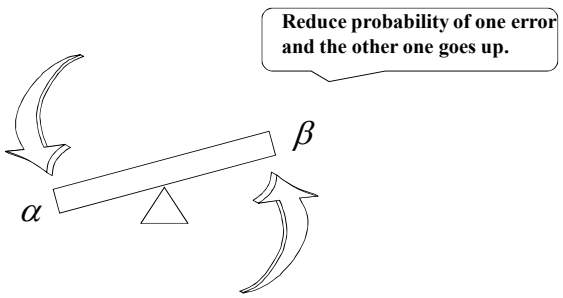
Type II Error

- **Type two Error** (false negative): β
- Error of not finding a difference when the difference is greater than the threshold or value of *delta* (Effect Size).
- Occur when the investigator fails to reject a null hypothesis that is not actually true (aquit a guilty)
- Depends on the definition of the threshold, i.e. the difference worth detecting, *delta*.

Power

- **1-Type two Error** 1- β
- The probability of rejecting the null hypothesis when it is actually false
- Usually power is set as 80% or 90% (power to find association if exists)

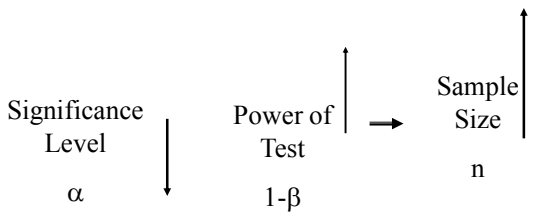
α & β Have an Inverse Relationship



Errors

1. They can never be avoided entirely.
2. The level depends on the importance of the issue.
3. Investigator can reduce them by increasing the sample size.

Relation between α, β and n



What are required for sample size estimation?

- Parameter (or outcome) of major interest
- Magnitude of difference in the parameter
- Variability of the parameter
- Bound of errors (type I and type II error rates)

Variability of the parameter of interest

- If the parameter is a continuous variable:
  - What is the **standard deviation** (SD) ?
- If the parameter is a categorical variable:
  - SD can be estimated from the proportion/probability.

Study design and outcome

- Single population
- Two populations

- Continuous measurement
- Categorical outcome
- Correlation

Sample Size

for

Continuous Response Variables

Hypothesis testing for means of 2 independent groups (t-test)

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(s_1^2 + s_2^2\right)}{\Delta^2}$$

برای هر گروه

$\Delta = Effect\ size$

s_1 = Sd of group 1

s_2 = Sd of group 2

Hypothesis testing for means of 2 independent groups (t-test)

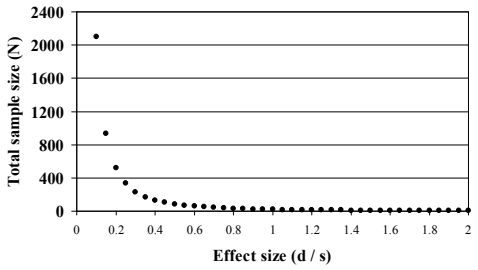
$$n = \frac{2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 s^2}{\Delta^2}$$

برای هر گروه

s = pooled standard deviation: $s^2 = \frac{s_1^2 + s_2^2}{2}$

α	1-α	β	1-β	$z_{1-\frac{\alpha}{2}}$	$z_{1-\beta}$	$\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2$
0.05	0.95	0.1	0.90	1.96	1.28	10.5
0.05	0.95	0.2	0.80	1.96	0.84	7.84
0.01	0.95	0.1	0.90	2.57	1.28	14.82
0.01	0.95	0.2	0.80	2.57	0.84	11.6
.	.					.
.	.					.

Sample size for *two means* vs.“effect size”



For a power of 80%, significance level of 5%

مثال

در بررسی تاثیر یک برنامه غذائی در کاهش کلسترول خون افراد مبتلا به هیپرکلسترومی، یک مطالعه آزمایشی انجام شده و نتایج زیر حاصل شده است:

	میانگین	انحراف معیار
تجربی	۲۳۰	۳۰
شاهد	۲۵۰	۲۵

الف) برای مطالعه اصلی در مجموع چه تعداد نمونه باید انتخاب کنیم تا با توان آزمون ۹۰ درصد و $\alpha=0/05$ حداقل اختلاف ۱۵ واحد بین میانگین دو گروه را معنی دار تلقی کنیم.

اگر بخواهیم اختلاف مشاهده شده در مطالعه آزمایشی را به عنوان اندازه اثر در نظر بگیریم تعداد نمونه چه تغییری خواهد کرد؟

$\alpha= 0.05 \qquad \beta=0.10 \qquad \Delta=۲۰$

مثال

مطالعه ای برای بررسی تاثیر کاهش نمک در رژیم غذایی، بر فشارخون افراد در دست طراحی است. بر اساس مطالعات قبلی انحراف معیار فشارخون در افراد با رژیم غذایی پرنمک ۱۲ و در افراد با رژیم غذایی کم نمک ۱۰.۳میلی متر جیوه بوده است.

چه تعداد نمونه انتخاب کنیم تا بتوانیم با سطح اشتباه ۵ درصد و توان ۹۰ درصد حداقل اختلاف ۸ میلی مترجیوه بین میانگین دو گروه را معنی دار تلقی کنیم؟

Hypothesis testing for paired sample means

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 s^2}{\Delta^2} \qquad \Delta = effect\ size$$

s = standard deviation of the differences

مثال

نتایج مطالعات نشان داده است که میانگین وزن مردانی که به تازگی بیماری قلبی آنها تشخیص داده شده است ۷۵ کیلوگرم بوده است. می خواهیم تاثیر نوعی تمرینات ورزشی را در کاهش وزن این گونه مردان آزمون کنیم.

تاثیر ورزش را زمانی معني دار تلقی خواهیم کرد که به طور متوسط وزن افراد را حداقل ده درصد (۷.۵کیلوگرم) کاهش دهد. با در نظر گرفتن توان ۸۰ درصد و سطح اشتباه ۵ درصد چه تعداد نمونه انتخاب کنیم؟ انحراف معیار اختلافات را ۱۲ کیلوگرم در نظر بگیرید.

Non Response

- The sample size refers to the number of complete responses needed.
- Non response must be estimated and taken into account to arrive to the final size

Total Sample Size

If design is stratified and Tests/estimations will be done at each strata. *The sample size applies to each strata.*

Otherwise all within strata comparisons or estimations will have larger errors or confidence intervals

Randomization Methods

- Parallel Groups
- Matched Groups
  - **Individual Matching**
  - **Group Matching**

جدول ارقام تصادفی

01703	49894	57579	98505	85008	98681	56862	41860
87556	95669	39885	31669	31460	96413	84398	31562
84254	60541	73290	54685	80208	77044	14771	33378
12429	43566	32578	38935	75460	98133	18386	12417
63055	26768	63609	92424	50808	95416	12795	50787
18348	79628	05778	72095	90754	90430	00791	38023
19827	95727	02372	23485	54372	89732	67768	72151
30236	52309	99971	44890	28222	92140	40703	16888
32160	42795	04959	73840	99110	07527	73725	19291
14832	30334	18047	38712	32931	85481	15378	25011
21151	02668	44154	95153	63213	70014	67531	52581
89677	82090	42211	75118	36233	25131	13314	33063
67129	12388	41678	51286	80948	91599	52652	02519
27808	23807	25424	35877	96308	45847	88287	88419
24646	88222	66395	24060	98186	81741	08675	36931
10030	79086	89464	28282	89252	14777	02033	42852

Comparing proportions

Hypothesis testing for 2 independent proportions

$$n = \frac{\left\{ z_{1-\frac{\alpha}{2}} \sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta} \sqrt{p_1(1-p_1) + p_2(1-p_2)} \right\}^2}{(p_1 - p_2)^2}$$

$$\bar{p} = \frac{p_1 + p_2}{2}$$

Example

- In a pilot study, a sample of 50 adult subjects suffering from a certain disease were compared to a sample of 50 comparable control subjects who were free of disease.
- 30 of the subjects with the disease (60%) and 25 of the controls (50%) were involved in industries using a specific chemical.
- How many subjects should be studied in each of the two groups to have 90% power of detecting the true difference between the groups if the hypothesis tested at the 5% level?

P1	P2	P_bar	$z_{1-\frac{\alpha}{2}}$	$z_{1-\beta}$	n
0.5	0.6	0.55	1.96	1.28	518
0.5	0.6	0.55	1.96	0.84	387
0.5	0.7	0.6	1.96	1.28	124
0.5	0.7	0.6	1.96	0.84	93
0.5	0.55	0.525	1.96	1.28	2092
0.5	0.55	0.525	1.96	0.84	1563

Estimation of an Odds - Ratio

$$n = \frac{Z^2_{1-\alpha/2}\left\{\frac{1}{p_1(1-p_1)} + \frac{1}{p_2(1-p_2)}\right\}}{\left[\ln(1-\varepsilon)\right]^2}$$

α = error type 1
ε = relative width of conf. interval
p_1 = proportion exposed in cases
p_2 = proportion exposed in controls

$$OR = \frac{p_1(1-p_2)}{p_2(1-p_1)}$$

Example

Estimation of an Odds Ratio

Example

Is living downwind from a factory a factor of risk for say alergic rhinitis?
The general population, i.e. upwind from the factory has an exposure prevalence of around 4% due to shifting wind directions etc; and a prevalence of rhinitis estimated at 15% . The downwind section has a prevalence of rhinitis estimated at 30% and an exposure of 15% .
We do not know the real values, these are guesses, otherwise we would not do the study.!!

We are interested in an OR of 2.0 with a 95% CI from 1.5 to 2.5.

Estimation of a Relative Risk

$$n = \frac{Z^2_{1-\alpha/2}\left\{\frac{1-p_1}{p_1}+\frac{1-p_2}{p_2}\right\}}{\left[\ln(1-\varepsilon)\right]^2}$$

α = error type 1
ε = relative width of confidence interval
p_1 = proportion exposed in cases
p_2 = proportion exposed in controls
$RR = p_1/p_2$

Estimation of a Relative Risk

The Relative Risk can be estimated from a follow up study.

• here p_1 and p_2 refer to incidences not prevalences. We need some estimate of the anual rate of disease in exposed and non exposed and proceed as per Odds Ratio.

Example

- An Epidemiologist compared, in a pilot study, a sample of 50 adult subjects suffering from a certain disease to a sample of 50 comparable control subjects who were free of disease. 30 of the subjects with the disease (60%) and 25 of the control (50%) were involved in industries using a specific chemical.
- How many subjects should be studied in each of the two groups to have 90% confidence of detecting the true difference between the groups if the hypothesis tested at the 5% level?