Biostatistical methods and common problems in biomedical science research : A short overview

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اطلاعات پزشکی و بهداشتی بدست آمده در پژوهش

تصمیم گیری پزشکی یا بهداشتی

Discussion

انواع مطالعات
انواع متغیرها
روشهای نمونه گیری
روش های تخصیص تصادفی

Why do you need a biostatistician?

Discussion

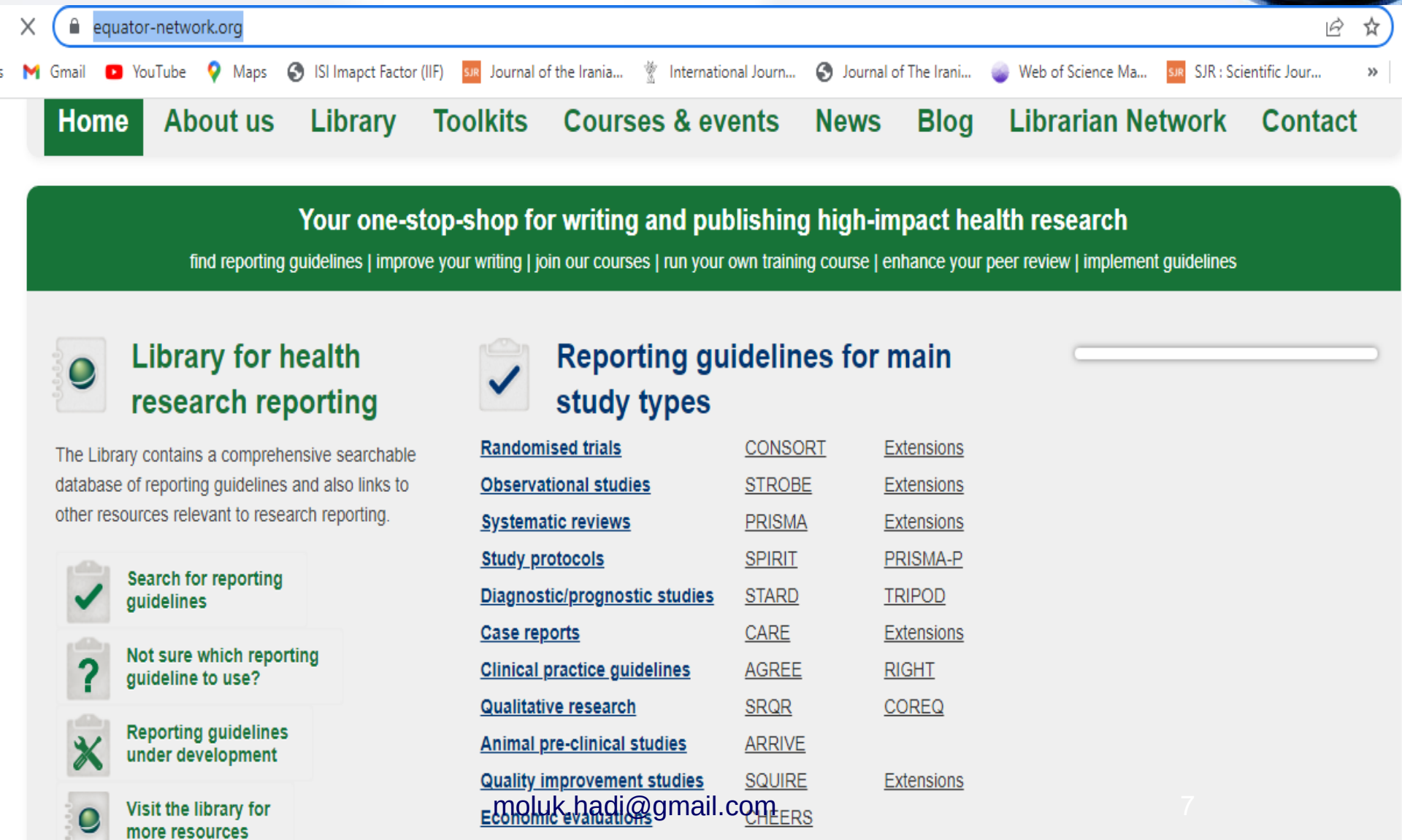
CHAMP: **CH**ecklist for statistical **A**ssessment of **M**edical **P**apers

Design and conduct				
1.	Clear description of the goal of research, study objective(s), study design, and study population	Yes	Unclear	No
2.	Clear description of outcomes, exposures/treatments and covariates, and their measurement methods	Yes	Unclear	No
3.	Validity of study design	Yes	Unclear	No
4.	Clear statement and justification of sample size	Yes	Unclear	No
5.	Clear declaration of design violations and acceptability of the design violations	Yes	Unclear	No
6.	Consistency between the paper and its previously published protocol	Yes	Unclear	No
Data analysis				
7.	Correct and complete description of statistical methods	Yes	Unclear	No
8.	Valid statistical methods used and assumptions outlined	Yes	Unclear	No
9.	Appropriate assessment of treatment effect or interaction between treatment and another covariate	Yes	Unclear	No
10.	Correct use of correlation and associational statistical testing	Yes	Unclear	No
11.	Appropriate handling of continuous predictors	Yes	Unclear	No
12.	Confidence intervals do not include impossible values	Yes	Unclear	No
13.	Appropriate comparison of baseline characteristics between the study arms in randomized trials	Yes	Unclear	No
14.	Correct assessment and adjustment of confounding	Yes	Unclear	No
15.	Avoiding model extrapolation not supported by data	Yes	Unclear	No
16.	Adequate handling of missing data	Yes	Unclear	No
Reporting and presentation				
17.	Adequate and correct description of the data	Yes	Unclear	No
18.	Descriptive results provided as occurrence measures with confidence intervals, and analytic results provided as association measures and confidence intervals along with P-values	Yes	Unclear	No
19.	Confidence intervals provided for the contrast between groups rather than for each group	Yes	Unclear	No
20.	Avoiding selective reporting of analyses and P-hacking	Yes	Unclear	No
21.	Appropriate and consistent numerical precisions for effect sizes, test statistics, and P-values, and reporting the P-values rather their range	Yes	Unclear	No
22.	Providing sufficient numerical results that could be included in a subsequent meta-analysis	Yes	Unclear	No
23.	Acceptable presentation of the figures and tables	Yes	Unclear	No
Interpretation				
24.	Interpreting the results based on association measures and 95% confidence intervals along with P-values, and correctly interpreting large P-values as indecisive results, not evidence of absence of an effect	Yes	Unclear	No
25.	Using confidence intervals rather than post-hoc power analysis for interpreting the results of studies	Yes	Unclear	No
26.	Correctly interpreting occurrence or association measures	Yes	Unclear	No
27.	Distinguishing causation from association and correlation	Yes	Unclear	No
28.	Results of pre-specified analyses are distinguished from the results of exploratory analyses in the interpretation	Yes	Unclear	No
29.	Appropriate discussion of the study methodological limitations	Yes	Unclear	No
30.	Drawing only conclusions supported by the statistical analysis and no generalization of the results to subjects outside the target population	Yes	Unclear	No

Biostatisticians & statistical consulting in clinical trials:

- Protocol design
- Sample size calculations
- Randomization schedules
- Statistical analysis plan
- Interim analyses
- Statistical analysis and interpretation
- Full and abbreviated clinical study reports

Protocol design



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statistical analysis plans for clinical trials to observational studies

Section/Item	Index	Description for clinical trials	Description for observational studies
Section 1: Administrative information			
Title and *study* registration	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and *study* acronym
	1b	Trial registration number	*Study* registration number
SAP version	2	SAP version number with dates	Unchanged
Protocol version	3	Reference to version of protocol being used	Unchanged
SAP revisions	4a	SAP revision history	Unchanged
	4b	Justification for each SAP revision	Unchanged
	4c	Timing of SAP revisions in relation to interim analyses, etc.	Timing of SAP revisions in relation to *planned repetitive* analyses
Roles and responsibility	5	Names, affiliations, and roles of SAP contributors	Unchanged
Signatures of:	6a	Person writing the SAP	Unchanged
	6b	Senior statistician responsible	Unchanged
	6c	Chief investigator/clinical lead	Unchanged
Section 2: Introduction			
Background and rationale	7	Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial	Synopsis of *study* background and rationale including a brief description of research question and brief justification for undertaking the *study*
Objectives	8	Description of specific objectives and hypotheses	Description of specific objectives and hypotheses, *including secondary objectives*
Section 3: Study methods			
Study design	9	Brief description of trial design including type of trial (e.g. parallel group, multi-arm, crossover, factorial and allocation ratio and may include brief description of interventions)	Brief description of *study* design including type of study *(e.g. case-control, cross-sectional or cohort study)*
Randomization	10	*Randomization details, e.g., whether any minimization or stratification occurred (including stratifying factors used or the location of that information if it is not held within the SAP)*	Not applicable
Power considerations	11	Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)	*In case of an unspecified sample size, provide power calculations for (at least) the primary analysis or present a detectable difference with a specified power**
Framework	12	Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis	Unchanged*
Statistical *repetitive* analyses and stopping guidance	13a	Information on interim analyses specifying what interim analyses will be carried out and listing of time points	Information on *repetitive* analyses specifying what *repetitive* analyses will be carried out and listing of time points*
	13b	Any planned adjustment of the significance level due to interim analysis	Any planned adjustment of the significance level due to *repetitive analyses*
	13c	Details of guidelines for stopping the trial early	Details of guidelines for stopping the *study* early
Timing of final analysis	14	Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up	Unchanged*
Timing of outcome assessments	15	Time points at which the outcomes are measured including visit "windows"	Unchanged
Section 4: Statistical principles			
Confidence intervals and *P*-values	16	Level of statistical significance	Unchanged*
	17	Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled	Unchanged*
	18	Confidence interval to be reported	Unchanged

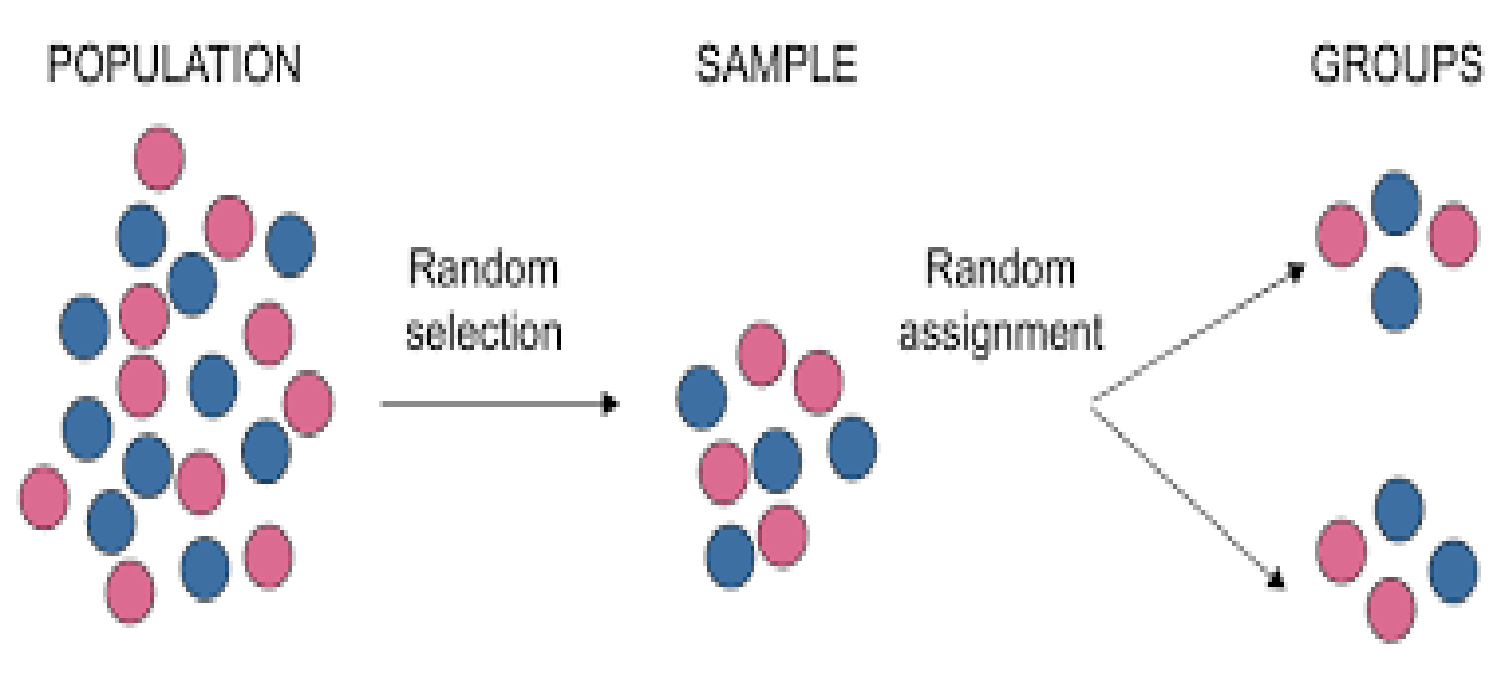
statistical analysis plans for clinical trials to observational studies

Section/Item	Index	Description for clinical trials	Description for observational studies
Adherence and protocol deviations	*19a*	*Definition of adherence to the intervention and how this is assessed including extent of exposure*	Not applicable
	19b	*Description of how adherence to the intervention will be presented*	Not applicable
	19c	Definition of protocol deviations for the trial	Definition of protocol deviations for the *study*
	19d	Description of which protocol deviations will be summarized	Unchanged
Analysis populations	20	Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety	Definition of analysis populations, e.g., per protocol, complete case, safety
Section 5: Study Population			
Screening data	21	Reporting of screening data (if collected) to describe representativeness of trial sample	Reporting of screening data (if collected) to describe representativeness of study sample
Eligibility	22	Summary of eligibility criteria	Unchanged
Recruitment	23	Information to be included in the CONSORT flow diagram	Information to be included in the *STROBE* flow diagram
Withdrawal/ follow-up	24a	Level of withdrawal, e.g., from intervention and/or from follow-up	Level of withdrawal, e.g., *dropouts after inclusion or refusal to be contacted for additional information*
	24b	Timing of withdrawal/lost to follow-up data	Unchanged
	24c	Reasons and details of how withdrawal/lost to follow-up data will be presented	Unchanged
Baseline patient characteristics	25a	List of baseline characteristics to be summarized	Unchanged
	25b	Details of how baseline characteristics will be descriptively summarized	Unchanged
Potential confounding covariates	–	–	*A description of potential confounding covariates and how these will be dealt with**
Section 6: Analysis			
Outcome definitions		List and describe each primary and secondary outcome including details of:	
	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	Unchanged
	26b	Specific measurement and units (e.g., glucose control, HbA_{1c} [mmol/mol or %])	Unchanged
	26c	Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, time to event, logarithm, etc)	Unchanged
Analysis methods	27a	What analysis method will be used and how the treatment effects will be presented	Unchanged*
	27b	Any adjustment for covariates	Unchanged
	27c	Methods used for assumptions to be checked for statistical methods	Unchanged
	27d	Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc	Unchanged
	27e	Any planned sensitivity analyses for each outcome where applicable	Unchanged*
	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	Unchanged*
Missing data	28	Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)	Unchanged*
Additional analyses	29	Details of any additional statistical analyses required, e.g. complier-average causal effect analysis	Unchanged

statistical analysis plans for clinical trials to observational studies

Section/Item	Index	Description for clinical trials	Description for observational studies
Harms	30	Sufficient detail on summarizing safety data, e.g. information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e. grade ¾ only, incidence case analysis, intervention emergent analysis	*Only applies when interventions are studied.* Sufficient detail on summarizing safety data, e.g. information on severity, expectedness, and *associations*; details of how adverse events are *scored*; how adverse event data will be analysed *and the follow-up time.**
Statistical software	31	Details of statistical packages to be used to carry out analysis	Unchanged
References	32a	References to be provided for nonstandard statistical methods	Unchanged
	32b	Reference to Data Management Plan	Unchanged
	32c	Reference to the Trial Master File and Statistical Master File	Reference to the *Study* Master File and Statistical Master File
	32d	Reference to other standard operation procedures to be adhered to	Unchanged

Randomization?



Random allocation in randomized clinical trials

Steps:

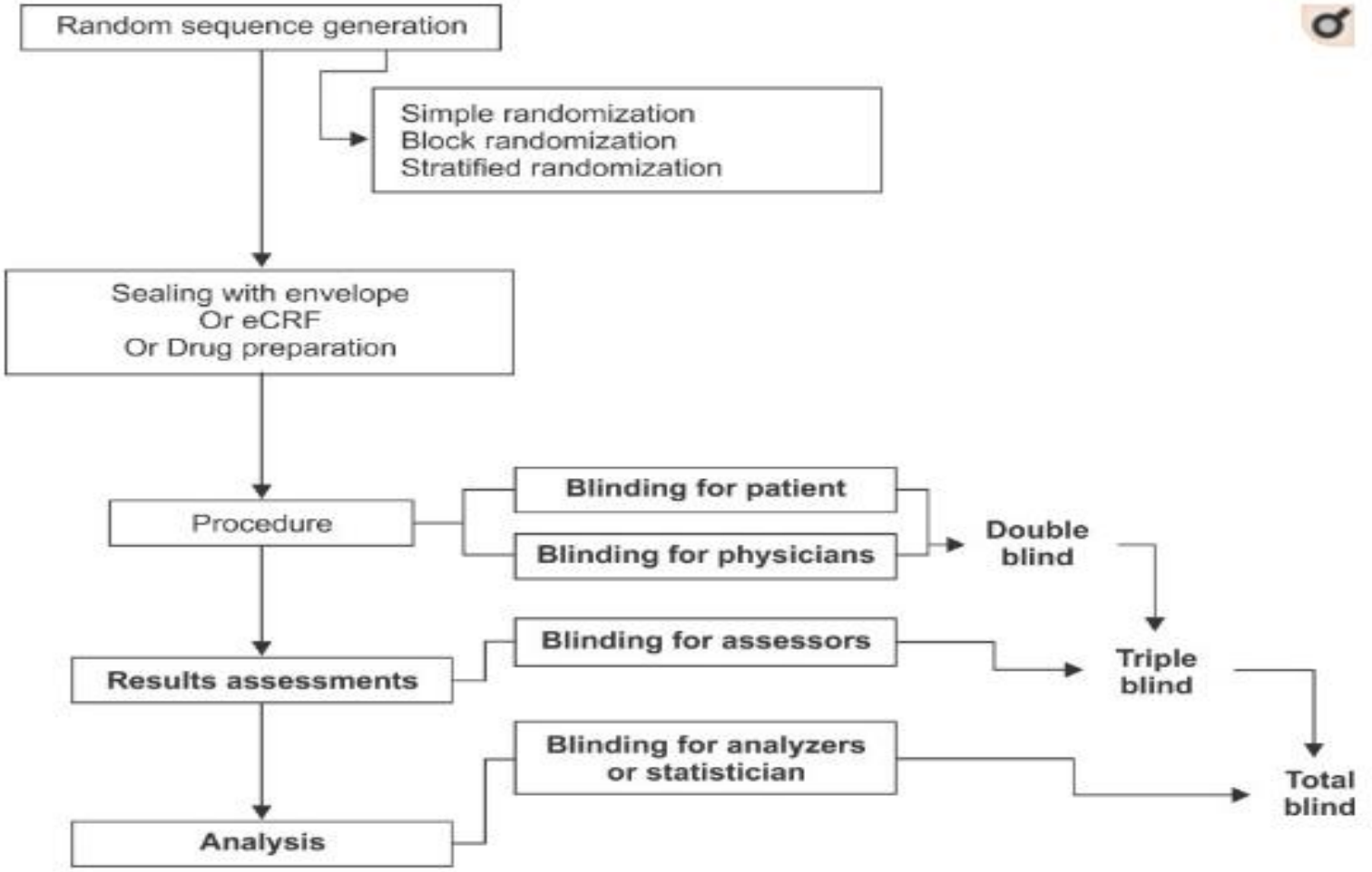
1. Random sequence generation
2. Allocation concealment
3. Running random allocation procedure

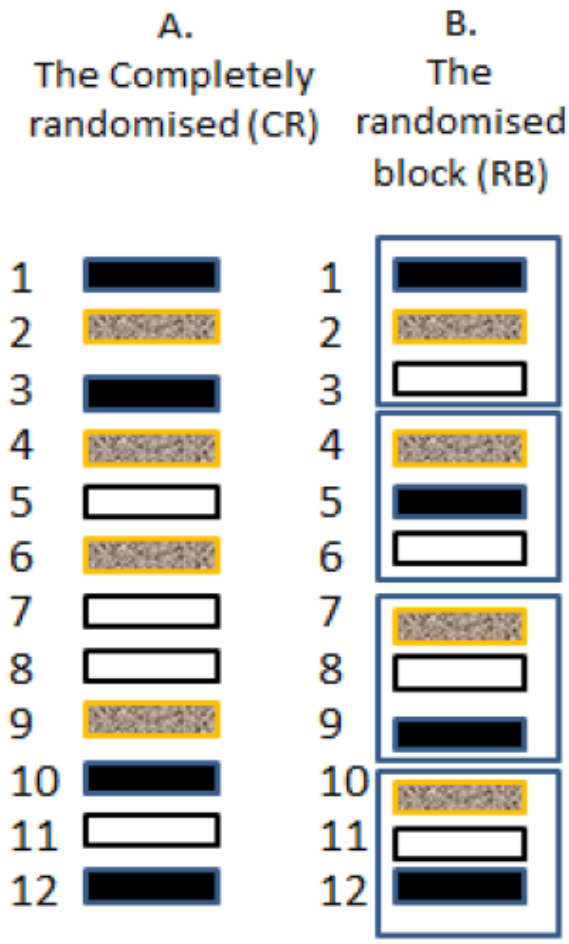
Random sequence generation:

- Simple randomization (unrestricted)
- Restricted:
  - Permuted block randomization
  - Random allocation rule
  - Replacement randomization
  - Stratified randomization
  - Minimization (Covariate adaptive randomization)

Online and software randomization

Randomization assignment procedure in RCT





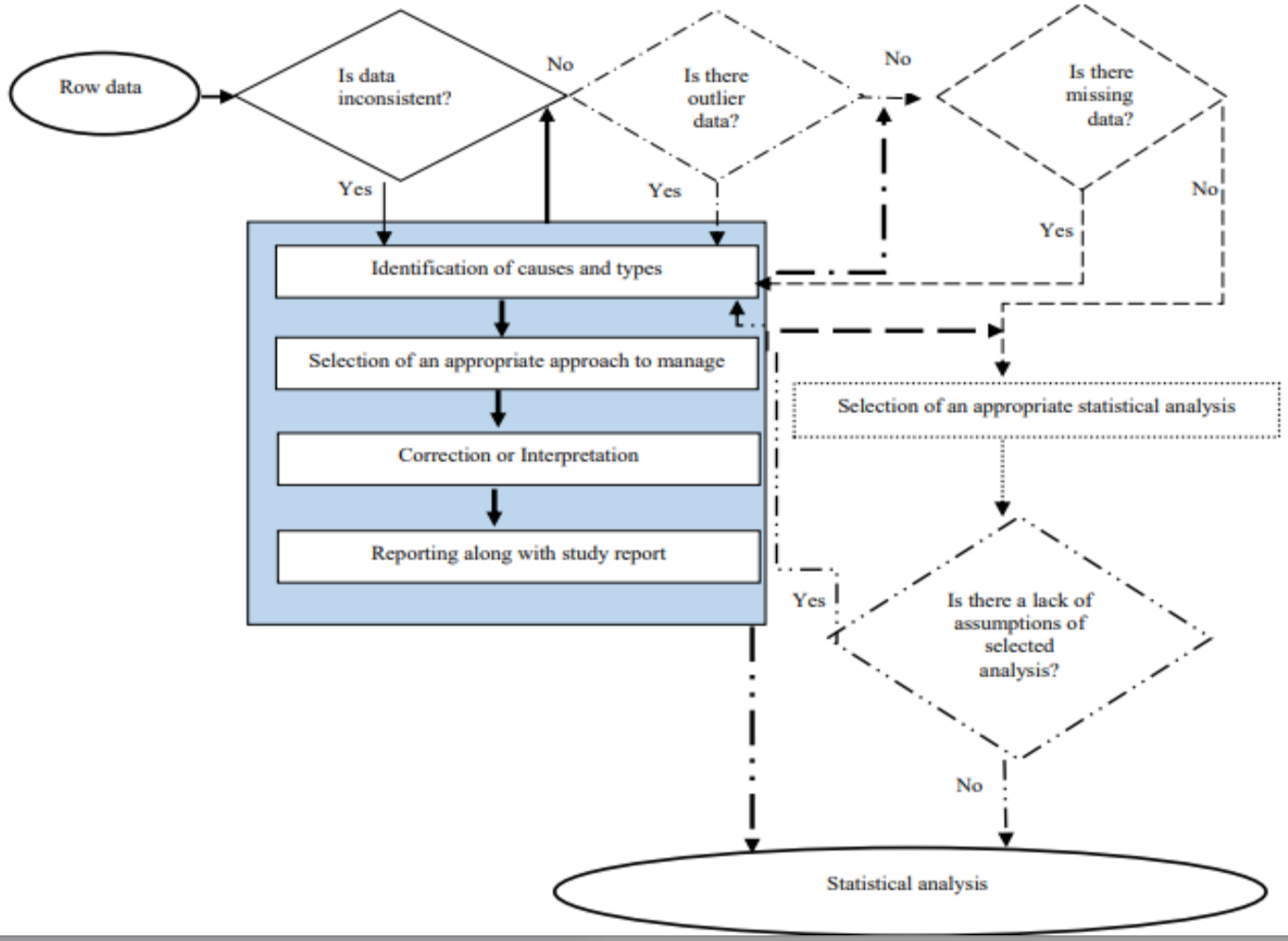
Whats happen after randomization?

Do you know about
“Propensity score matching in randomized clinical trials”?

Discussion based on article:

Lettor to editor-fa-random allocation

Cleansing and preparation of data for statistical analysis



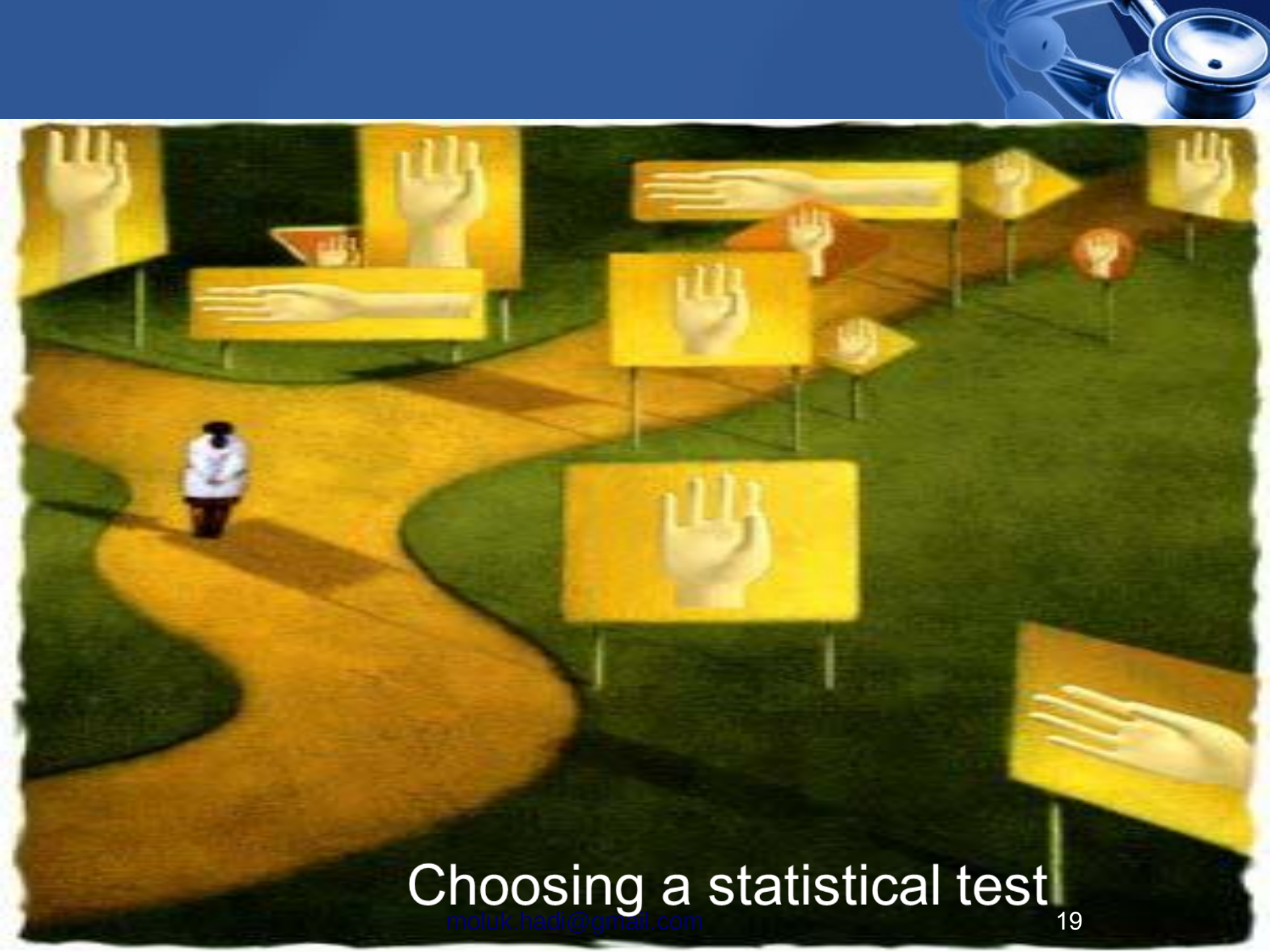
Start with descriptive statistics

Summary statistics to describe a study population or group

Variable Distribution	Summary Statistic(s)
Continuous (normally distributed)	Mean (standard deviation)
Continuous (not normally distributed)	Median (interquartile range)
Ordinal	Median (interquartile range)
Dichotomous	Proportion
Nominal	Relative proportions

Graphical data Summarization

Variable type	Graph type
Nominal categorical	Bar graph, pie chart
Ordinal categorical	Bar graph, pie chart
Continuous numerical	Histogram, scatter plot, box-plot
Discrete numerical	Box-plot, stem-leaf plot


Choosing a statistical test

Basic statistical methods for different type of variables

Outcome	Assumption	Statistical test
Numerical data		
One sample mean	Normal distribution	One sample t-test
One sample median	Not normally distributed	One sample median test or sign test/signed rank test
Two independent means	Normal distribution	Two sample t-test
Two independent means	Not normally distributed	Wilcoxon-Mann-Whitney test (Wilcoxon rank sum test)
Two correlated means	Normal distribution	Paired t-test
Two correlated means	Not normally distributed	Wilcoxon signed rank test
Independent more than two means	Normal distribution	ANOVA test
Independent more than two means	Not normally distributed	Kruskal Wallis test
Correlated (or repeated) more than two means	Normal distribution	Repeated measure ANOVA
Relationship between two numerical variables	Normal distribution	Pearson correlation test
Relationship between two numerical variables	Not normally distributed	Spearman correlation test
Categorical data		
One proportion test		Binomial test
Relationship between two categorical variables		Chi-square test
Relationship between two categorical variables, but one or more cells have expected value less than 5		Fisher's exact test
Test same categorical outcome on matched pairs		McNemar test
Binary outcome measured repeatedly		Repeated measure logistic regression

define two main elements to help identify the appropriate statistical method for a study:

1. What is being measured in the study? (Study variables)

2. How are these variables related? (Purpose of analysis)

Choosing a statistical test

1. Choosing a statistical test to determine if the distribution of the outcome variable is different across two or more explanatory subgroups

1. Choosing an appropriate statistical model to examine if an outcome variable is associated with one or more explanatory variables

Outcome Variable	Explanatory Variable: Dichotomous (Unrelated)	Dichotomous (Related)[1]	Three or More Subgroups (Unrelated)	Three or More Subgroups (Related)[1]
Continuous (normally distributed)	Two-sample *t* test	Paired *t* test	Analysis of variance (ANOVA)	Mixed-effects model for repeated measures
Ordinal, Continuous (not normally distributed)	Wilcoxon rank sum test	Wilcoxon signed rank test	Kruskal-Wallis test	Friedman test, Skillings-Mack test
Categorical	Chi-square test, Fisher exact test[2]	McNemar test	Chi-square test, Fisher exact test[2]	Cochran *Q* test[3]

[1]Analyses in which the groups of the explanatory variable are related may be better addressed using multilevel modeling techniques, and thus the investigator should consider consulting with a biostatistician to help appropriately incorporate these analytic techniques.

[2]Fisher exact test should be used if at least one expected count is less than 5.

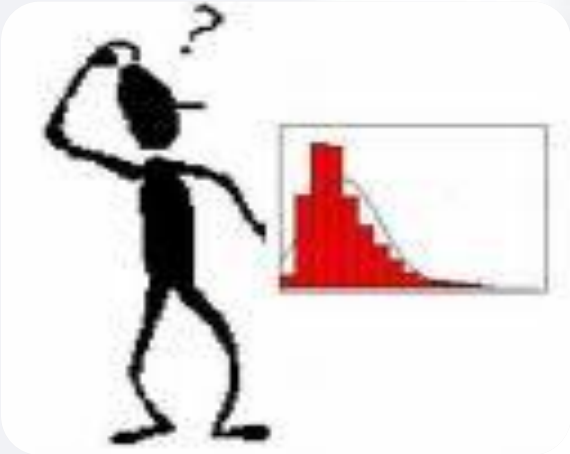
[3]For dichotomous outcome only.

Outcome Variable	Measure of Association	Regression Model[1]	Notes
Continuous variable	Difference in means	Linear regression	Residuals should meet assumptions, otherwise the continuous outcome may need to be broken into categories and analyzed using multinomial logistic regression.
Ordinal variable	Odds ratio	Ordinal logistic regression	Model should meet proportional odds assumption.
Count variable	Incidence rate ratio	Poisson regression	The count variable should meet the Poisson assumptions; otherwise, other models may be used including negative binomial regression, zero-inflated or zero-truncated models, etc.
Dichotomous variable (case-control analysis)	Odds ratio	(Unconditional) logistic regression	Because of the case-control study design and thus the inability to determine prevalence of the outcome of interest, the odds ratio is the only measure of association that can be used.
Dichotomous variable (matched case-control analysis)	Odds ratio	Conditional logistic regression	If additional confounding is still present after matching, multivariable conditional logistic regression may be used.
Dichotomous variable (cross-sectional analysis)	Prevalence ratio (relative risk)	Log binomial regression	Prevalence odds ratio using logistic regression may also be used; however, if the prevalence of the outcome exceeds 10%, the odds ratio will overestimate the relative risk. Poisson regression with a robust variance estimator can be used if the log binomial regression fails to converge.
Dichotomous variable (longitudinal analysis with a discrete time interval)	Cumulative incidence ratio (relative risk)	Log binomial regression	Poisson regression with a robust variance estimator can be used if the log binomial regression fails to converge.
Dichotomous variable (longitudinal time-to-event analysis)	Hazard ratio (relative risk)	Cox proportional hazards model	Model should follow the proportional hazards assumption.
Nominal variable	Odds ratio	Multinomial logistic regression	Odds ratios for the different categories will be compared with a common reference category.

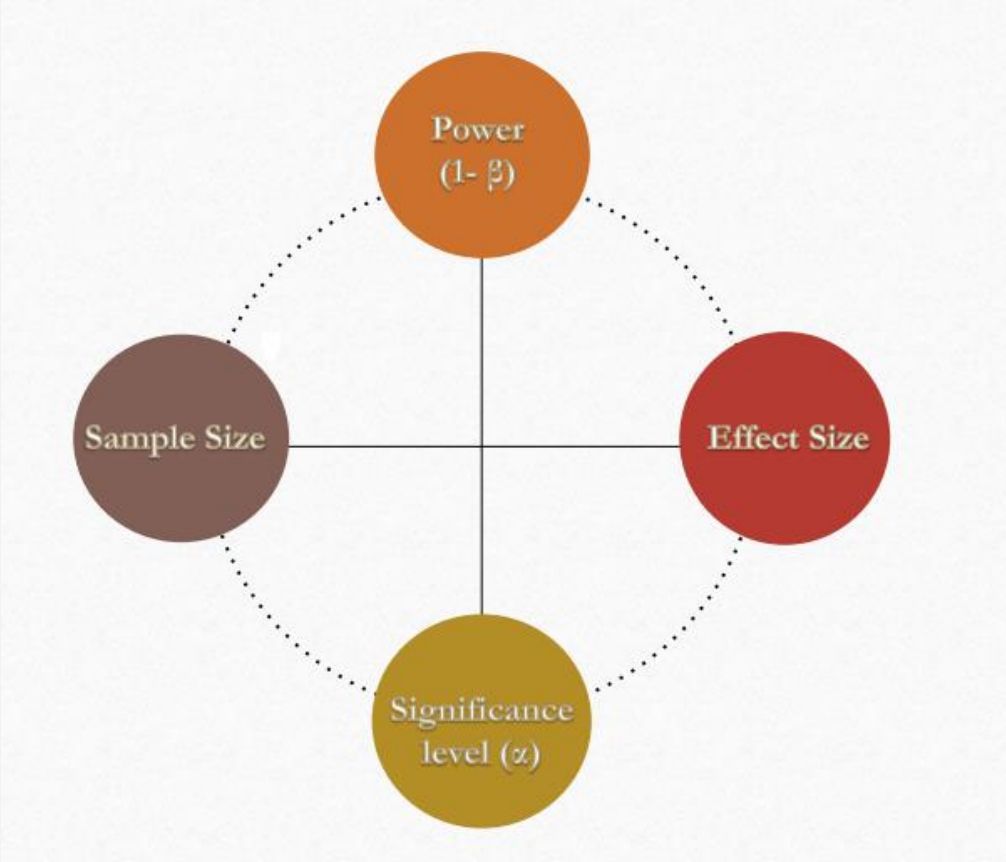
[1]Regression models can incorporate one or more categorical or continuous explanatory variables.

Reporting Results of Statistical Tests:
based on example APA

Discussion



Statistically significance?
or
clinically significance?



Effect size calculation

psychometrica.de/effect_size.html

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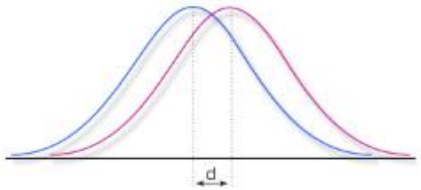
- Effect Size
- cNORM
- Interpolation of Norm Values
- Norm Score Calculator
- Significance of Correlations
- Test Characteristics

Suche

New: Continuous Norming with R (cNORM)
R package for generating continuous test norms in psychometrics and biometrics and for analyzing the model fit

cNORM

Computation of Effect Sizes



Statistical significance specifies, if a result may not be the cause of random variations within the data. But not every significant result refers to an effect with a high impact, resp. it may even describe a phenomenon that is not really perceivable in everyday life. Statistical significance mainly depends on the sample size, the quality of the data and the power of the statistical procedures. If large data sets are at hand, as it is often the case f. e. in epidemiological studies or in large scale assessments, very small effects may reach statistical significance. In order to describe, if effects have a relevant magnitude, effect sizes are used to describe the strength of a phenomenon. The most popular effect size measure surely is Cohen's d (Cohen, 1988), but there are many more.

Here you will find a number of online calculators for the computation of different effect sizes and an interpretation table at the bottom of this page. Please click on the grey bars to show the calculators:

1. Comparison of groups with equal size (Cohen's d and Glass Δ) +

2. Comparison of groups with different sample size (*Cohen's d, Hedges' g*) +

3. Effect size for mean differences of groups with unequal sample size within a pre-post-control design +

4. Effect size estimates in repeated measures designs +

5. Calculation of d and r from the test statistics of dependent and independent t-tests +

Any Question!