Principi e la metodologia della ricerca clinica

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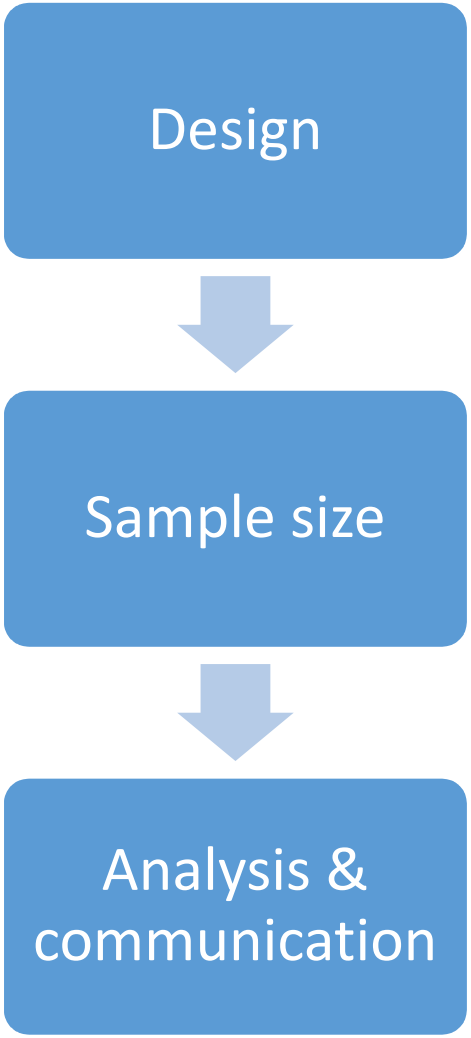
Selected Milestones in Health Care Interventions and Delivery Strategies and in Research Methods.*		
Decade	**Milestones in Health Care Interventions and Delivery Strategies**	**Milestones in Research Methods**
1940s	Antibiotic agents (penicillin and streptomycin), kidney dialysis, general anesthesia, radiotherapy, first heart-pump machine, influenza vaccine, Papanicolaou (Pap) smear to detect cervical cancer, cortisone, intraocular lens implants for cataracts	First large-scale, randomized, controlled trial
1950s	Cardiopulmonary resuscitation, kidney transplantation, vaccination against poliomyelitis, chlorpromazine for schizophrenia, Zeiss fluorescence microscope, antitubercular therapy, cardiac pacemaker, artificial heart valve, successful open-heart bypass surgery	Case–control methodology, Kaplan–Meier survival estimator
1960s	Charnley's hip replacement, coronary-artery bypass grafting surgery, heart transplantation, oral contraceptive pill, prenatal diagnosis of Down's syndrome	Explanatory versus pragmatic trial concept, data and safety monitoring, growth of observational research methods committees
1970s	Cure for some childhood cancers; neonatal intensive care; computed tomography; coronary angiography; quality measures in health care; ambulatory surgery; vaccinations against smallpox, measles, mumps, rubella, and pneumonia	Cox proportional-hazards model; meta-analysis; ascendancy of randomized, controlled trials; statistical stopping rules
1980s	Insulin therapies for diabetes mellitus, thrombolysis for heart attacks, antihypertensive drugs, magnetic resonance imaging, robotic surgery, permanent artificial-heart implant, deep-brain electrical stimulation system, first laser surgery on the human cornea, hepatitis B vaccine	Propensity score; large, simple trials; prognostic models (e.g., Framingham risk score), growth of decision and cost-effectiveness analyses
1990s	Coronary stents, triple therapy for the acquired immune deficiency syndrome, introduction of biologics, "physician extenders," facial transplantation, vaccine against hepatitis A, first rotavirus vaccines	Evidence-based medicine, cumulative meta-analysis, reporting guidelines (CONSORT statement), ascendancy of registries, electronic health records, Markov chain Monte Carlo sampling for Bayesian inference
2000s	Human Genome Project completed, drug-eluting coronary stents, FDA guidance on patient-reported outcomes, minimally invasive techniques for surgery, human papillomavirus vaccine to prevent cervical cancer	Trial registration (ClinicalTrials.gov), comparative-effectiveness research, implementation science, large-scale genomic research, reproducible research
2010s	Genomics, epigenomics, individualized medicine, health information technology, emergence of telehealth, meaningful-use initiatives, Affordable Care Act becomes law	Patient-centered outcomes research

Gabriel & Normand, Getting the Methods Right — The Foundation of Patient-Centered Outcomes Research, NEJM, 2012 787-781

- **Rationale and aims**
  - Scientific relevance
  - Social relevance
- **Methods**
  - Correspondence between aims and design
  - Scientific merit of design
  - Safety of design
  - Feasibility/burden of design
- **Statistics**
  - Sample size justified according to design and aims
  - Statistical analysis according to design
- **Logistics**
  - Randomization and/or enrollment specified
  - CRO involvement
  - Safety and adverse events monitoring
  - Privacy
- **Genetics**
  - Study conduction and data bank exploit plan



Statistics and Ethics

Quality Data + Ethics = GCP

Data and Reported Results are Credible and Accurate = quality data

Rights, Integrity, and Confidentiality of Study Subjects are Protected = Individual targeted ethics

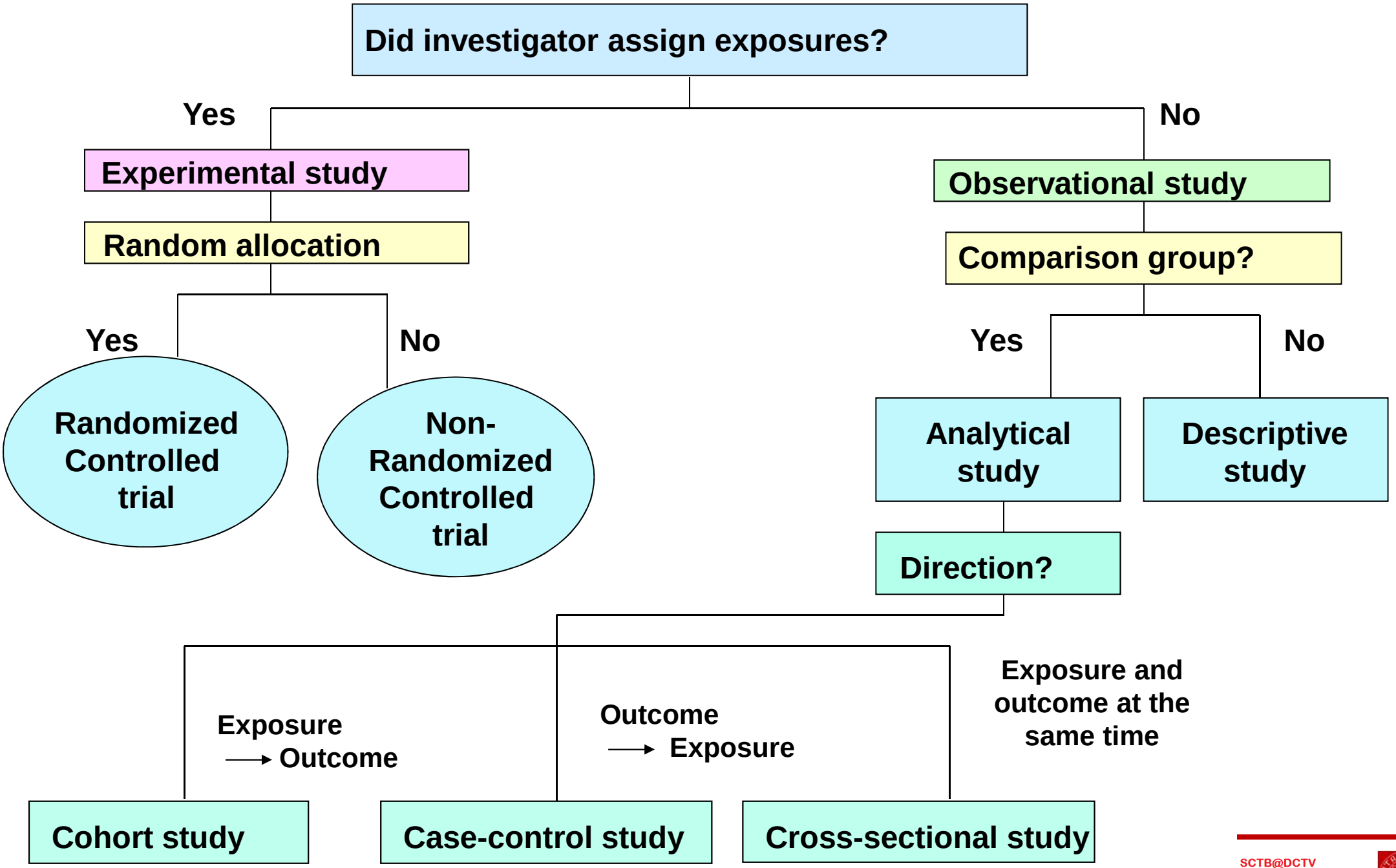
Ethics

Ethical considerations in statistical methodology

- Study design and experimental methodology
  - It is unethical to include people in a study where poor design and/or poor methodology will lead to less-than-optimum quality data and therefore less-than-optimum quality answers to the study's research question.
- Sample-size estimation
  - A trial requires sufficient participants to answer the research question without exposing them unnecessarily to the risks of the experimental therapy.
- Early termination of trials
  - Data monitoring committees (DMCs), independent groups charged with reviewing interim data from clinical trials, face difficult ethical challenges when deciding whether a clinical trial should be terminated early (US Department of Health and Human Services, FDA, 2006).
- Communicating trial results
  - Researchers have an ethical responsibility to report information accurately and fully in clinical communications, as these directly impact patient care.

Correct study design is absolutely essential from both scientific and ethical perspectives when conducting clinical trials. If a study's design cannot lead to the collection of data that can be analyzed meaningfully, no meaningful information about the investigational drug can be gained.

Participants in clinical trials have the legitimate expectation that their participation in the trial will help advance our knowledge of the investigational drug, and if the study's design cannot possibly provide additional knowledge about the drug their expectation is not fulfilled (Turner, 2007).



Grimes and Schulz, The Lancet 359:57-61 (2002)

Observational studies taxonomy

- **Case control studies** examine the relationship between an attribute and a disease by comparing those with and without the disease with respect to the presence of the attribute or level of exposure to it.
- **Cohort studies** examine the relationship between exposure to a factor or factors and the probability of the occurrence of a disease (or other outcome) by observing large numbers of people over a period of time and comparing incidence rates of the disease (or outcome) in relation to exposure levels. A cohort study may be a clinical cohort study (for example, where a group of patients with a given disease is followed to examine the prognosis).
- **Cross-sectional studies** examine the relationship between diseases (or other healthrelated characteristics) and other variables of interest in a defined population at one particular point in time, by collecting health and other information concerning members of the population. These include questionnaires or surveys done for research purposes.
- **Case reports** are reports of cases from health or disability service or research settings.
- **Case series** describe a set of cases of a disease (or similar problem). For example, a clinician may assemble a case series on a topic of interest, such as an unexpected adverse effect experienced by patients taking a particular medication.
- **Descriptive studies** examine the existing distribution of variables in populations. For example, analyses of cancer registry data or emergency department data by person, place or time

For (drug) clinical trials

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Working group of pharmaceutical industry experts and regulatory authorities from the European Union, Japan, and the United States
- Aim to produce a single set of technical requirements for the registration of new drug drug products to streamline development
- Reduce or obviate duplicate testing
- More economical use of human, animal and material resources
- Eliminate unnecessary delays in the availability of new medicines

ICH guidelines of statistical interest

E3	Structure and Content of Clinical Study Reports
E4	Dose Response Information to Support Drug Registration
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6	Good Clinical Practice
E7	Clinical Trials in Special Populations: Geriatrics
E8	General Considerations for Clinical Trials
E9	Statistical Principles for Clinical Trials
E10	Choice of Control Group in Clinical Trials
E11	Clinical Investigation of Medicinal Products in the Pediatric Population
E12A	Clinical Evaluation of Drugs by Therapeutic Categories: Antihypertensives
M4	Common Technical Document (format for summary documents)

www.ic

Considerations on clinical trials

- Primary endpoint(s)
- Study design
  - Tools to against bias
  - Choice of design
  - Type of comparison
- Sample size calculation
- Interim analyses
- Statistical analyses
  - Analysis population and handling of missing data
  - Statistical methods
  - Control of type I error (multiplicity issue)

Disadvantages of Randomized Control Clinical Trial

1. Generalizable Results?
   - **Subjects may not represent general patient population – volunteer effect**

2. Recruitment
   - **Twice as many new patients**

3. Acceptability of Randomization Process
   - **Some physicians will refuse**
   - **Some patients will refuse**

4. Administrative Complexity

For observational studies

ALLEGATO 1

Linee guida per gli studi osservazionali sui farmaci

31-3-2008 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA *Serie generale* - n. **76**

Tabella 1: Tipologia di studi osservazionali

1) studi di coorte prospettici
2) altri studi osservazionali a) studi di coorte retrospettivi b) studi caso-controllo c) studi solo su casi ("*case cross-over*" e "*case series*") d) studi trasversali e) studi di appropriatezza

In ciascuno degli studi indicati possono essere anche presenti obiettivi di valutazione economica dell'uso dei farmaci (farmacoeconomia).

2. Protocollo

Ogni Studio osservazionale deve fondarsi su un protocollo in cui gli obiettivi ed il disegno dello studio devono essere definiti in modo chiaro e coerente. Nel protocollo presentato deve essere chiaramente valutabile l'ipotesi della ricerca, i risultati attesi, il tipo di studio osservazionale, la

scelta della dimensione campionaria, le informazioni che saranno raccolte, l'eventuale coinvolgimento della struttura e/o degli operatori sanitari, le risorse richieste, l'origine del finanziamento, le modalità di partecipazione e di informazione rivolte al soggetto. Modifiche sostanziali al protocollo dello studio dovranno essere notificate ai Comitati etici secondo quanto previsto per quella specifica tipologia di studio.

The STROBE initiative

http://www.strobe-statement.org/

OPEN ACCESS Freely available online

PLOS MEDICINE

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration

Jan P. Vandenbroucke[1], Erik von Elm[2,3], Douglas G. Altman[4], Peter C. Gøtzsche[5], Cynthia D. Mulrow[6], Stuart J. Pocock[7], Charles Poole[8], James J. Schlesselman[9], Matthias Egger[2,10*] for the STROBE Initiative

METHODS		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants (b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2008, **63**, pages 967–971 doi:10.1111/j.1365-2044.2008.05539.x

A case series of the use of the ProSeal laryngeal mask airway in emergency lower abdominal surgery

J. Fabregat-López,[1] B. Garcia-Rojo[1] and T. M. Cook[2]

Summary

The ProSeal laryngeal mask airway (PLMA) has been used routinely for anaesthesia and for difficult airway management including airway rescue in non-fasted patients. Compared with the classic laryngeal mask airway the PLMA increases protection against gastric inflation and pulmonary aspiration, by separating the respiratory and gastro-intestinal tracts. The PLMA has potential advantages over use of the tracheal tube including smoother recovery, reduced pharyngolaryngeal morbidity and even reduced postoperative pain. We report a series of patients scheduled for emergency appendicectomy, without other risk factors for regurgitation, managed with the PLMA. Anaesthesia was induced and maintained with remifentanil, target controlled propofol and rocuronium. A series of 102 cases were managed without complications and high rates of first time placement of the PLMA (inserted over a suction tube placed in the oesophagus). With careful patient selection the PLMA may offer an alternative airway for use by experienced anaesthetists in patients undergoing minor lower abdominal surgery.

Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2008, **63**, pages 1163–1166

Editorial

Gambling with ethics? A statistical note on the Poisson (binomial) distribution

In a recent issue of the journal, Fabregat-López et al. [1] report a study that raises both ethical and

bution or 'probability density functions' (all these terms are very closely related) [5]. The Appendix to this article outlines some of the mathematics involved, which indeed seem very dense. The purpose of the next

birds) is zero; at the other extreme is when an infinite number of observations are made and the probability is 1 (i.e. we are certain to see a complication or bird if we look infinitely long or hard). In between is the

Risk of aspiration (most serious risk in PLMA technique) with tracheal intubation and conventional rapid sequence induction is about 1/1000 and probably closer to 1/4000

Table 1 Minimum number of observations (or patients) needed in a study to observe at least one event, when the prevalence of the event is between 0.005 and 5% (which approximates many common events or complications of anaesthetic interest). The examples are purely illustrative, approximate and random, and do not imply that this is a precise prevalence of the stated problem, nor that these are the most important problems in anaesthesia. Note that the numbers needed to observe > one event will be considerably greater.

Prevalence of event (e.g., a complication) (%)	Example of risk or complication	Minimum number of observations required to observe at least one event	
		With > 95% probability	With > 99% probability
~0.005	Awareness with general anaesthesia [18]	~6000	~10 000
~0.1	Prevalence of eclampsia [19]	~3000	~5000
~0.25	Serious complications due to cervical plexus block [20]	~1250	~2000
~0.5	Failed intubation in obstetric practice [21]	~600	~1000
~1	Incidence of postdural puncture headache [22]; incidence of cricothyroidotomy in US emergency departments after attempted tracheal intubation [23]	~300	~500
~3	Conversion to general anaesthesia with deep cervical block [20]	~100	~170
~5	Serious complications after carotid endarterectomy [20]; mortality after pulmonary aspiration [24]	~60	~100

Sample Size Issues

- **Fundamental Point**

  Trial must have sufficient statistical power to detect differences of clinical interest

- High proportion of published negative trials do not have adequate power

  Freiman et al, NEJM (1978)

  50/71 could miss a 50% benefit

Statistical Considerations

Null Hypothesis (H_0):

No difference in the response exists between treatment and control groups

Alternative Hypothesis (H_a):

A difference of a specified amount (Δ) exists between treatment and control

Significance Level (α): Type I Error

The probability of rejecting H_0 given that H_0 is true

Power = (1 - β): (β = Type II Error)

The probability of rejecting H_0 given that H_0 is not true

Seeding trials

Better Regulation of Industry-Sponsored Clinical Trials Is Long Overdue

Matthew Wynia and David Boren

Conduct Scientifically Irrelevant "Seeding Trials"
Some studies, such as "seeding trials," are not intended to answer a research question at all, but only to create marketing data or to raise practitioners' awareness and use of a new drug.[44] It is not clear how common such trials are — they are sometimes called "formulary acceptance" or "provider experience" trials — but some have been criticized as little more than kickback schemes for prescribing physicians, who are paid to "enroll" patients.[45] "Seeding trials" are marked by "the use of a design that does not support the stated research goals...recruitment of investigators not because they are experts or leading researchers but because they are frequent prescribers of competing products in the same therapeutic class...disproportionately high payments given to investigators for their work...sponsorship of the studies by the company's sales and marketing division rather than its research department... minimal requirements for data...[and] the collection of data that are of little or no value to the company."[45] Patients are presumably never informed of the true (i.e., marketing) intent of these "trials."

A sign of a seeding trial is an unrealistically small effect + a very large sample size

Clinical criteria for multiple targets

Primary Endpoints	Secondary Endpoints	Target (significance)	Multiplicity testing
$p \geq 1$	$s \geq 1$	One primary	No need
$p \geq 1$	$s \geq 1$	Al least one primary	Need
$p \geq 1$	$s \geq 1$	All primary	No need
P1, P2, P3	$s \geq 1$	Either P1 or both P2 and P3	Need
P1, P2, P3	$s \geq 1$	Either (P1 and P2) or (P1 and P3)	Need
$p = 1$	$s \geq 1$	One primary, the secondary marginally significant	Need
$p \geq 1$	$s \geq 1$	Hierarchical significance among primary	No need
$p \geq 1$	$s \geq 1$	*k* primary, the remaining marginally	Need
$p \geq 1$	$s \geq 1$	Complex (usually hierarchy between primary and secondary)	Need

Sample Size Adjustment for Non-Compliance

Simple Model -

Compute unadjusted N

- Assume no dropins
- Assume dropout proportion R
- Thus $P_C^* = P_C$

  $P_T^* = (1-R)\,P_T + R\,P_C$

- Then adjust N

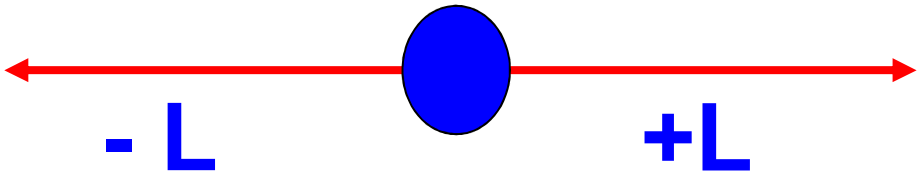
$$N^* = \frac{N}{(1-R)^2}$$

- Example

R	$1/(1-R)^2$	% Increase
.1	1.23	23%
.25	1.78	78%

Sample Size for observational studies

$$n = \frac{4PQ}{L^2}$$



- P = Estimated prevalence (percentage)
- Q =1-P
- L = Allowable Error

Precision estimate

- A survey is to estimate prevalence of influenza virus infection in school kids
- Suppose the available evidence suggests that approximately 20% (P=20) of the children will have antibodies to the virus
- Assume the investigator wants to estimate the prevalence within 6% of the true value (6% is called allowable error; L)
- The required sample size is
- $n = (4 \times 20 \times 80) / (6 \times 6) = 177.78$
- Thus approximately 180 kids would be needed for the survey

… once incorrect procedures become common, it can be hard to stop them spreading through the medical literature like a genetic mutation …

oug Altman