The language of randomized clinical trials

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1. Introduction

The vocabulary of clinical trials is a hybrid mixture of terms and phrases principally from medicine, statistics, biostatistics, epidemiology, and bioethics. It is the product of practitioners of trials, methodologists and theoreticians concerned with the design, conduct, and analysis of trials, and regulators of trials. Mastery is made difficult by differences in language conventions depending on type of trial and speciality area.

However, mastery of the vocabulary of clinical trials is not sufficient to speak "clinical trials". One must also master the art of "reading between the lines". If someone says a trial is *randomized*, is the person using the term in the lay sense of usage or in a rigorous sense? If investigators say *results were analyzed by intention to treat* do they mean what they say? What do they mean by *dropout*, *withdrawal*, and *lost to followup*?

Controlled Clinical Trials (the journal) and the Society for Clinical Trials came into being because of the need for better communication among trialists and for a better and more precise language in the practice of trials.[1,2,3] The drive has been fueled in recent years by the push for evidence-based medicine. Its foundation rests on randomized trials and on means to harvest information from collections of like trials (meta-analysis) to provide the evidentiary base for medicine. That push has provided the impetus for promulgation of various guidelines for reporting trials.[4,5,6,7,8,9,10,11]

2. On the language of relativity

The witch, in Snow White, turned to a mirror for absolute truth. Trialists' mirrors are not so powerful. At best, they reveal relative truths and then only grudgingly. Hence, one must also master the language characteristic of relativists to speak "clinical trials" fluently.

A relativists' talk is sprinkled with signed terms such as better or worse, increase or decrease, or good or bad where the point of reference may be obscure, vary, or shift. When it comes to summarizing results they have options. They can present in Joe Friday (of TV Dragnet fame) fashion or as a Texas used car salesman.

Suppose a trial done to determine whether a new treatment is useful in reducing mortality associated with a chronic disease. Suppose a sample size of 200, with 100 persons randomized to the test treatment and a corresponding number randomized to the control treatment. Suppose each person is treated and followed for one year and that at the end of the trial 4 deaths have been recorded – 3 among control-assigned persons and 1 among test-assigned persons.

The Joe Friday dry bones characterization of the results might be as follows: *A total of 4 deaths were observed – 3 among the 100 control-assigned patients and 1 among the 100 test-assigned patients. The estimated mortality rates for the two treatments were 3 and 1 per 100 person years of followup, respectively. The difference is not significant.* The gee whiz characterization of the same results might be: *There were 67% fewer deaths in the test-treated group of patients than in the control-treated group. The difference represents a 3-fold reduction in mortality. The results suggest that the treatment may be useful in reducing the risk of mortality.*

2. Language of relativity

The art form in the latter approach is to concentrate on the relative difference without mention of the base numbers needed for measuring the difference. The trick is use of relative terms to create the illusion of substance without a baseline – not unlike what we encounter everyday in the merchandizing world with *sale*, *discount*, *$10 dollars off*, and *everything reduced 20%*. To be sure, the gee whiz format makes for more entertaining reading, but it is not entertainment one seeks when reading journals. The better papers are fact-filled and written in the dry bones format. They can be as interesting to read as watching paint dry, but the facts and details are golden when trying to understand the results.

Good writers make certain that finished papers have the necessary numbers and underlying counts when ratios, rates, or percentages are reported. They steer clear of the "fold" mode of characterizing results when it is illusionary (as in the example above) and take care to define what is meant by signed terms such as more or less, big or small, or better or worse.

3. Random: The term

Random, as an adjective, in everyday speech is used in reference to chance or happenstance in regard to some event (eg, in characterizing a tornado as a *random act of God*) or in reference to some sequence of occurrences or numbers having no discernable pattern or order. In rigorous usage it refers to a process or procedure that generates output characterized by a series of discrete events having known probabilities of occurrence. The line of demarcation between lay and rigorous use lies in whether the probability base exists.

Randomization is the act of assigning persons to treatment according to a schedule set down using some random process having a known probability base and that is used as set down. Both conditions are necessary for assignments to qualify as *randomizations*. The tests of soundly constructed and administered randomization schemes include the following:[12]

- **Documentablity** (achieved by use of documented system for generating random numbers, eg, via a table of random numbers[13] or with certain pseudorandom number generators)
- **Reproducibility** (schedule can be reproduced given the particulars of generation)
- **Unpredictability** (future assignments not predictable from past assignments)
- **Concealment** (schedule concealed to clinic personnel)
- **Controlled release** (assignments remain unknown to clinic personnel until person has consented, been judged eligible, necessary baseline data collected and recorded, and person and study physician ready to administer the assigned treatment)
- **Invariant use** (schedule of assignments used in the order set down)
- **Accountability** (one-to-one correspondence between assignments released and persons counted as randomized; assurance that a person is counted as randomized when the assignment is revealed to clinic personnel and is counted to the treatment assigned, regardless of course of treatment)
- **Indeliability** (indelible audit trail of transactions; to check for departures from the schedule as set down)

3. Random: The term

The labels, *random*, has an aura of respectability. Hence, there is a tendency to use it loosely. Readers need to be watchful for such uses. A reasonable rule of thumb is to assume the lay form of usage in the absence of detail such as listed above.

In an ideal world, trials not meeting tests as outlined above would not be labeled as *randomized*, but life is not so obliging. The term *nonrandomized* is rarely used, even if it applies. Trials where the treatment is selected by the treating physician or physician and patient are typically refereed to as open – to be read as a euphemism for *nonrandomized*. Readers beware!

4. Terminology: Comments and recommendation

The lexicon of trials is a clutter of redundant and contradictory terms. It comes about because of tendencies of groups to invent and create new terms without much regard for existing terminology.

Ideally, groups would start from a list of accepted terms when starting a trial. But, there is no authority in charge of vocabulary and such glossaries do not exist. The best that can be hoped is that groups will create and maintain their own, that they will use them, and that they will establish internal editorial standards to assure uniformity and consistency of terminology.

If language is sloppily used or debased in documents created in design and conduct of a trial, that "slop" and debasement will carry over into the finished report. Hence, the road to a better and more precisely used language in trials has to start with groups when designing and implementing trials. The effort to "standardized" reports of trials, while to be applauded, is unlikely to produce the desired end product in the absence of a "standard lexicon" for when trials are designed and conducted.

The list below is in that direction. It is a mixed bag of definitions, comments, and usage recommendations. It includes troublesome terms in common usage as well as terms preferred or recommended for usage. The definitions and usage notes are from or adapted from a more comprehensive work entitled *Clinical Trials Dictionary: Terminology and usage recommendations.*[14]

analysis by treatment assignment Used to characterize a counting and analysis philosophy considered necessary for reliable analysis of results from randomized trials; also known as **intention to treat analysis** (see **intention to treat** for comment). Accompany use with sufficient detail or references to make usage clear.

4. Terminology

baseline	Subject to misuse; limit to measurements or observations at or prior to randomization; avoid in other contexts or indicate usage departures from norm.
blind, **blinded**	Use **mask** or **masked**; blind has undesirable and inappropriate connotations; single-masked, double-masked, triple-masked.
center	Use as collective term to include all types of centers represented; avoid as a synonym for clinic in **multicenter trials** ; see **multicenter**.
collaborative, **cooperative**, as in collaborative trial	Not a suitable synonym for multicenter because of implication that collaboration is not required for single-center trials.
control treatment	A treatment that serves as a basis for comparison; in trials may be active or inactive. Active treatments include standard care or use of a study treatment intended to produce a positive or negative treatment effect; inactive treatments include placebo treatment, sham treatment, nil treatment, nontreatment, and null treatment.
controlled (adj)	1. Constrained, monitored, or watched. 2. Any system of observation and data collection that is designed to provide a basis for comparing one group with another, such as provided in a parallel treatment design with concurrent enrollment to the different study groups represented in the design. Technically redundant as a modifier for randomized trial; all randomized trials are controlled.
design variable	The variable used for determining or justifying sample size in planning a trial, usually also the **primary outcome**.
drop-in	Used in reference to person receiving a **study treatment** other than the one indicated by randomized to; avoid absent definition
dropout	Subject to misuse; often loosely used as a label, absent defining detail. In proper usage, a characterization applied to a person no longer able or willing to return to a study clinic for scheduled followup visits; not operationally equivalent to **lost to followup**. Observations that can be made only during clinic visits by direct examination of a patient are lost so long as person remains a dropout but those that can be made by other means (eg, by telephone if the person does not refuse contact) need not be. Technically, even persons who drop out and refuse contact

can be tracked for life-death status without direct contact. See also **missed visit** and **treatment noncompliance**.

endpoint — Subject to confusion because of implied operational meaning. Generally best avoided in favor of an operationally neutral term (such as **outcome** or **event**), especially in treatment and prevention trials where persons remain under treatment and followup after an "endpoint" (usually the case). Most “endpoints” in those settings are not “end” indicators. As a rule, protocols are written so as to require treatment and followup over a specified period of time regardless of most intercurrent events. The only "endpoint" with operational meaning is death in those settings.

evaluable (adj); capable of being evaluated for some purpose or end — When used in relation to results (eg, *results in this paper are based on evaluable patients randomized to treatment*), best read: *Readers beware! Results and conclusions based on a select subset of patients; counts and analyses not in conformity with recognized as necessary with **analysis by treatment assignment**).*

event, eg, as in adverse event, morbid event — In regard to observations made on study patients, an occurrence, incident, or experience, especially one of importance or significance; use instead of **endpoint** in reference to binary type outcome measures.

informed consent — Use consent. One can hope that consent is informed but, absent supporting data, the modifier is more an expression of hope than of fact.

intention to treat — Jargon; who knows about intentions? Avoid because focus is on intention rather than on what is actually done.

intention to treat analysis — Use **analysis by treatment assignment**.

lost to followup — Often loosely used; see **dropout**.

multicenter (adj) — Preferred to **collaborative** or **cooperative** as modifier for trial because of implication that single-center trials are "noncollaborative" or "noncooperative".

missed visit — A scheduled visit not made within the allowable time window

negative (adj) — In regard to results: 1. Of or relating to the absence of effect. 2. Of or relating to an effect that is in a direction opposite to that desired or

expected. Reserve for use in the second sense. Use nil or some other appropriate term for uses in the sense of defn 1.

off-protocol (adj) 1. Of or relating to a person not receiving the assigned treatment. 2. Of or relating to a person for whom use of the assigned treatment has been suspended or terminated for medical or other reasons, eg, intolerable side effects, development of some other disease condition requiring other forms of treatment, or because of treatment suspension. 3. Of or relating to a person not treated or observed in accordance with the study protocol. 4. Of or relating to a person who is no longer willing or able to remain under followup. 5. Being a dropout. Subject to confusion; avoid absent definition.

off-study (adj) 1. Of or relating to something done or to be done that is not part of a study protocol. 2 **off-protocol** Subject to confusion; avoid absent definition.

open (adj) In trials: 1. Of or relating to treatments assigned or administered as chosen or dictated by the treating physician or patient. 2. Of or relating to a system of treatment assignments in which assignments are known or can be determined by those responsible for administration of the treatments, eg, a scheme in which the assignments to be made are posted in a clinic for all to see or an odd-even method of treatment assignment involving unmasked treatments. 3. Not masked. 4. Of or relating to a trial still enrolling patients. Avoid in the absence of defining detail. Avoid as euphemism for nonrandomized (defn 1).

open-label trial Euphemism for unmasked trial.

open trial See **open** (adj).

placebo 1. A pharmacologically inactive substance given as a substitute for an active substance, especially when the person taking or receiving it is not informed whether it is an active or inactive substance. 2. A pill made of lactose or some other pharmacologically inert substance. 3. Any medication considered to be useless, especially one administered in pill form; a useless or ineffective treatment. Limit use to settings involving administration of a pharmacologically inactive substance given as a substitute for an active substance. Avoid nonsensical use, eg, *placebo patient* in reference to a patient assigned to placebo treatment.

placebo treatment 1. A treatment involving the use of a placebo. 2. An ineffective or useless

	treatment. Limit use to defn 1; avoid in the absence of a placebo medication. Not the same as sham treatment. Do not equate to absence of treatment. Usually placebo treatment is in addition to the care ordinarily given.
primary outcome	1. The event or condition a trial is designed to treat, ameliorate, delay, or prevent. 2. The foremost measure of success or failure of a treatment in a trial. Usually synonymous with **design variable** but not always.
principal investigator (PI)	Multiple meanings, use with caution. *Principal* (adj) means most important, foremost, chief, or head. Avoid in uses where there is more than one principal, eg, as a designation for heads of centers in a multicenter trial. Avoid to the exclusion of other like persons, eg, as a label for persons heading study clinics in multicenter trials to the exclusion persons heading other kinds of centers in such trials. Avoid as a synonym for **study chair**.
random, **randomized**, **randomization**	Do not use as a characterization except in settings where there is an explicit or implied mathematical basis for supporting the usage. Use other terms implying less rigor than implied by **randomization**, such as haphazardization, quasirandomization, or chance, when that basis is not present or evident.
single-center (adj)	Of, relating to, or comprised of one center. Use in contradistinction to multicenter.
sham treatment	Reserve for use in relation to bogus procedures designed to mimic an actual procedure, eg, as in certain types of surgery trials. Not to be confused with **placebo treatment**
study treatment	1. A **treatment** that is the focus of study, especially in an experimental setting; **test treatment**. 2. Any treatment, including a **control treatment**, applied in a trial as part of a study protocol; also treatment arm.
subject	Best avoided in favor of patient or some other term suggestive of the partner relationship required for consent, treatment, and followup.
subgroup	A subpart or subset of a **study population** distinguished by a particular characteristic or set of characteristics (eg, males under age 45 at entry).
subgroup analysis	1. Any data analysis focused on a selected subgroup. 2. Analysis aimed at

characterizing **observed differences** among different subgroups, eg, **comparison** of **treatment differences** in a **trial** for different subgroups of **patients** defined by sex, age at entry, and other **baseline characteristics**. 3. A form of **exploratory data analysis** aimed at trying to identify a subgroup of persons that account for an observed difference, eg, such an analysis in a trial to determine whether or not an observed **treatment difference** can be accounted for by some **subgroup**. Not the same as data dredging. Data dredging is value-laden and pejorative. Subgroup analysis is neutral in connotation and is descriptive of a process. Analysis involving subgroups formed using entry demographic and other baseline characteristics is an essential part of the analysis process for a trial. The analyses are done to determine whether or not it is reasonable to regard the treatment effect observed as being homogeneous (ie, independent of entry and other important baseline characteristics). The analysis has bearing on conclusions reached from the trial. Evidence of qualitative or quantitative treatment by baseline characteristic interaction obligates the trialist to temper or qualify the conclusion accordingly. A treatment effect cannot be assumed to be homogeneous across subgroups absent analyses aimed at addressing the question of homogeneity of treatment effect. Subgroup analyses become forms of data dredging if results of such analyses are used to identify "significant" differences without regard to the number of subgroups studied or when the results are presented so as to suggest that the difference is the result of clinical insight regarding an underlying disease process.

test treatment 1. Any of the **study treatments** in a **trial**, except those designated as **control treatments**. 2. The treatment or one of the treatments (except **control treatments**) being or to be evaluated in a trial. 3. **treatment variable** ***Usage note***: Typically, in medical settings the term refers to a **drug**, **device**, or **procedure** administered or performed for its presumed therapeutic or diagnostic value. However, the term can also be used in broader settings. It may refer to nontherapeutic schemes or regimens applied to well people in nonmedical settings, eg, in a **prevention trial** involving counseling schemes intended to produce lifestyle changes.

treatment Preferred generic label for the experimental variable in clinical trials; see **study treatment**, **test treatment**, and **control treatment**.

treatment group The group of persons **randomized** to a specified treatment; also sometimes study group (not recommended) and treatment arm (not recommended).

4. Terminology

treatment compliance — The degree to which a person or the person's treater follows the assigned treatment regimen. Rarely all or none; generally best viewed and described as a continuum, especially in trials involving repeated applications of treatment.

treatment failure — 1. The failure of a treatment as administered to produce the desired effect or result. 2. Such a failure as observed, inferred, or declared by a study physician or other study personnel from measurements, evaluations, or observations on the person or treatment unit in question and accompanied by cessation of that treatment or a treatment switch. 3. A person no longer receiving the assigned treatment; especially because of concerns regarding safety or efficacy. Use with caution because of presumption connoted by *failure*.

withdrawal — Subject to misuse; avoid in the absence of definition.[6] Do not use as synonym for dropout or loss to followup (see **dropout** above). Use best reserved for actions taken by study personnel to forego or halt use of the assigned treatment, usually because of lack of benefit or because of ill-effects (eg, as used in the Consolidated Standards of Reporting Trials (CONSORT)[4]. Withdrawal from treatment does not remove the effect of treatment. One can be withdrawn from treatment but not from its effects.

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