JOHNS HOPKINS
UNIVERSITY

Center for Clinical Trials

Department of Biostatistics
Department of Epidemiology
Department of International Health

Department of Medicine
Department of Ophthalmology
Oncology Center

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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: On the definition of clinical trials

The NIH, in a release dated 23 October 2014, announced it was changing its definition of clinical trial (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html) to make the distinction between clinical trials and clinical research studies clearer.

Clinical research, as defined on the NIH glossary for grants and funding (dated 20 March 2013), is:

> Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes:
>
> - mechanisms of human disease
> - therapeutic interventions
> - clinical trials
> - development of new technologies
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> Epidemiological and behavioral studies.
> Outcomes research and health services research.

The definition of clinical trial in the announcement is:

> A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

The previous definition was (http://grants.nih.gov/grants/policy/nihgps_2013/nihgps_ch1.htm#glossary; last updated 23 October 2013):

> A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g., imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test itself imposes more than minimal risk for the subjects.

The definition proposed is similar to that of the WHO for registering trials on its platform:

> any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

The definition of trials used by the ICMJE for defining trials subject to registration as requirements for publication is:

> any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome.
> (http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html)

As a writer of sorts, I have an aversion to “ly” words. Usually, they add nothing but clutter. Indeed, I told my kids years ago that if I ever got to be president my first executive order would be to ban all "ly" words, except early.

My "ly" affliction leads me to ponder whether there is any difference between “prospectively assign” and “assign”? One surmises "prospectively" is in the definition to make it clear that assignments are forward in time, but the direction of time is clear in the definition so the word, for me, is clutter.

But more to the point, why not use "treatment" instead of "intervention" to characterize the variable of interest in the definition?

Intervene as a verb means to come or occur between two times or events. Technically, anytime I interact with a person I am intervening in that person's life. Hence, examining a person in an observational study is a form of intervention. "Treatment" is a more accurate characterization of what goes on in trials.

If I had the power to edit the NIH definition of clinical trial I would get rid of “prospectively” and change "intervention" to "treatment" to produce the following:

> A trial in which human beings are assigned to treatments (which may include placebo or no treatment at all) to evaluate the effects on health-related outcomes.

Ironically, "trial" is not a study type on ClinicalTrials.gov. The two principal types are "interventional" and "observational"; defined as follows:

> INTERVENTIONAL STUDY (or Clinical Trial): A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions.
> OBSERVATIONAL STUDY: A clinical study in which participants identified as belonging to study groups are assessed for biomedical or health outcomes. Participants may receive diagnostic, therapeutic, or other types of interventions, but the investigator does not assign participants to specific interventions (as in an interventional study).

The tendency of definition writers to use imprecise terms when more precise terms exist is frustrating to those concerned with the language of trials. The tendency, no doubt, is born of desires on the part of researchers to minimize anxiety of patients when describing what they want to do. "Study" and "intervention" is less ominous sounding then "trial" and "treatment".

We see evidence of this in publications of results of trials. Of 1,097 publications indexed by NLM as randomized controlled trial and multicenter study and published in the first half of 2014, about 25% had study or studies as a principal word in the title.

Technically, the best word to describe a study in which persons or groups of persons are assigned to treatments is "experiment" (Clinical Trials Dictionary; 2nd edition; Wiley 2012):

1. A procedure or test preformed to discover an effect or law, to test or establish a hypothesis, to demonstrate a known fact or law, or to measure an effect.
2. A purposeful process involving the control, management, or manipulation of an experimental variable toward some end.
3. trial
4. test
5. A procedure or process changed because of circumstance or order; fortuitous experiment; natural experiment; social experiment.

But that word is rarely used in consents because of the fear and trepidation it evokes.

Trying to capture the all of trials via one definition, no matter how carefully crafted, is impossible. The above mentioned dictionary has over 100 entries with trial as a base term. The entry "clinical trial" reads as follows:

1. An experiment done involving persons as study subjects for the purpose of assessing the safety and/or efficacy of a treatment, especially such an experiment involving a clinical event as an outcome measure, done in a clinical setting, and involving persons having a specific disease or health condition.
2. An experiment involving the administration of different study treatments in a parallel treatment design to a defined set of study subjects having a given disease or a defined health condition and done to evaluate the efficacy and safety of a test treatment in ameliorating or curing that disease or health condition; any such trial, including those involving healthy persons, undertaken to assess safety and/or efficacy of a treatment or health care procedure (e.g., usefulness of monitoring fetal heart rate on pregnancy outcome; usefulness of different dietary schemes in the prevention of hypertension).
3. An uncontrolled trial involving treatment and followup of people given a particular treatment.
4. The first use(s) of a new treatment in human beings.
5. A publication type in the National Library of Medicine indexing system defined as: Pre-planned clinical study of the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favorable and unfavorable effects (NLM; 1997).

As a lexicographer of sorts I am reminded of a passage in Samuel Johnson's preface to *A Dictionary of the English Language* (1755)

> *It is the fate of those who toil at the lower employments of life, to be rather driven by the fear of evil, than attracted by the prospect of good; to be exposed to censure, without hope of praise; to be disgraced by miscarriage, or punished for neglect, where success would have been without applause, and diligence without reward.*
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> *Among these unhappy mortals is the writer of dictionaries; whom mankind have considered, not as the pupil, but the slave of science, the pioneer of literature, doomed only to remove rubbish and clear obstructions from the paths of Learning and Genius, who press forward to conquest and glory, without bestowing a smile on the humble drudge that facilitates their progress. Every other author may aspire to praise; the lexicographer can only hope to escape reproach, and even this negative recompense has been yet granted to very few.*

Whoa is me.