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# CLINICAL TRIALS

Medical experiments on human beings are called trials. The intervention must be potentially beneficial and not harmful. This could be drug, surgical procedure, medical device, behavioural change, process of care, or any other such regimen. When carefully conducted, clinical trials are the fastest and safest way to evaluate efficacy and safety of a new regimen under controlled conditions.

Although clinical trials have attained central place in product development, many breakthroughs in medicine occurred without such trials. Recent example is demonstration of bacterial origin of gastric ulcer by Marshall who infected himself with H. pylori and developed gastritis. Since the subjects are humans in clinical trials, a large number of issues crop-up ranging from ethics to profound variations. A human experimentation can not be conducted unless sufficient reasons for doing so are present. A noninvasive procedure does not cause much anxiety except for time and cost but an invasive procedure has potential to cause harm to the health of the patient.

Regimen research environment is changing. Safety is increasingly getting precedence over efficacy. Aspirin with its marvelous utility in cardiac problems may not have made it to the market today with its side-effect of gastric ulcer. The current paradigm seems to be that a new regimen should be free of toxicity while also be efficacious. Perhaps risk-benefit has taken a back seat for daily drugs. For special drugs such as against cancer, side-effects are tolerated and risk-benefit becomes relevant.

Trials can be done on patients coming to a clinic, or on a community in the field at large. Although clinical trials are mostly for therapeutic modality, they can also be prophylactic regimen such as for prophylactic amnioinfusion for meconium-stained amniotic fluid at the time of child-birth, or can be for a diagnostic procedure such as comparison of prostatic specific antigen levels and ultrasound images for prostate cancer. A trial for a screening procedure can also be conducted in a clinic setup although it is generally conducted in a community. The intervention in case of diagnostic trials is not an external agent but a procedure that can help reach the correct diagnosis and thus help to choose the right course of treatment.

Therapeutic trials raise important ethical issues because they generally involve exogenous material that may have side-effects, and may not be beneficial at all relative to the existing modes of therapy. For this reason, extreme care is exercised in conducting such trials. Among them, one is that the regimen must pass through rigours of preclinical phases. First of them of course is a laboratory phase to examine the biochemical properties of the test regimen, and second is an experiment on suitable animal model that can simulate human conditions. A clinical trial is embarked upon only after achieving success in these phases. For research on a therapeutic regimen, make sure that these phases are conducted with convincing success. This requirement is sometimes waived when the therapy or its variation is already in use for some other condition and the trial is to examine its use in a new set of conditions.

Sometimes trials are done to demonstrate equivalence rather than superiority of one regimen over the other. When the efficacy of a new regimen does not differ by more than a prespecified clinically relevant amount from the existing regimen, it is called **therapeutically equivalent**. If the course of the disease or of improvement pattern over a period of time is nearly the same, they are called **bioequivalent**. For therapeutic equivalence, only the outcome is considered. For bioequivalence the entire course is considered.

Efficacy is always related to a particular outcome. Terms such as recovery and discharge are vague outcomes. They must be specified either in terms of measurements such as glomerular filtration rate for kidney diseases, in terms of images such as x-ray of dislocation of joint, or in terms of any such objective criterion. Also the duration after which the outcome is to be assessed should be specified—within a day, within a week, or what. This applies to death also. Everybody dies but if a death occurs three months after a surgery, should this be ascribed to the surgery? Follow-up period for different outcomes of interest must also be fully specified.

Phases of clinical trials
Validity of clinical trials

Adapted from:
Basic Methods of Medical Research, Fourth Edition, 2018 by A. Indrayan
Details at
http://www.medicalbiostatistics.com/Medical_Docs/MedicalResearchBook.pdf