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The modern day equivalent of controlled trials was done by James Lind almost 275 years ago onboard the Salisbury at sea:

> *On the 20th of May 1747, I took twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. ... Two of these were ordered each a quart of cyder a-day. Two others took twenty-five gutts of elixir vitriol three times a day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of seawater. ... Two others had each*

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> *two oranges and one lemon given them every day. ... The two remaining patients, took the bigness of a nutmeg three times a-day. ...*
>
> *The consequence was, that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them, being at the end of six days fit for duty (James Lind, 1753).*

Lind's trial is why British sailors are nicknamed limeys, but it would be 50 years after his experiment before the British Navy stocked ships with lime containing fruits. A harsh reality underscoring the time it takes for results from trials to be incorporated into everyday life. A reality worth keeping in mind as we await vaccines for COVID-19.

The truth is that trials are usually too small to yield reliable information. In the hyperbola of President Trump "it is a disgrace!" or in the words of Oliver Hardy "another fine mess".

A trial (aka controlled trial) is an experiment done to provide information on the merits of a treatment or procedure relative to another treatment or procedure. The modifier "clinical" distinguishes trials involving humans from those involving animals and to make it clear that the trial involves people under clinical care. Generally "clinical" is understood in the context of usage and is unnecessary.

"Controlled" as in "controlled trial" implies a system of observation and data collection designed to provide a basis for comparing one group with another.

"Randomized", as in "randomized trial" means that the treatment a person receives is chosen by some process equivalent to flipping a coin. Randomization is the sine quo non of trials because, when properly designed and done, it assures that assignments are bias free. Free of influence of wishes or desires of the person being studied and of clinic personnel administering treatments.

Treatments are "test" or "control". The test treatment, typically a drug, device, substance, or procedure administered or performed for its presumed therapeutic or diagnostic value. The control treatment is the treatment against which the test

treatment is compared. It may be medically active or inactive. Active control treatments include standard care treatment and best medical judgment treatment. Inactive control treatments include placebo and sham treatments.

Treatments may be masked or unmasked, meaning identity of the treatment is known or unknown to designated persons. Masking is done to reduce the risk of bias in evaluation and in data collection. Masking or blinding may be single or double; single if only the person being treated or the persons doing the treatment is masked; double if both the person being treated and the persons doing the treatment are masked.

Masking is not always possible, for example in most surgery trials. It is most commonly practiced in drug trials were it is possible to produce pills or tablets that are identical in appearance and taste to the test drug. To work pills have to be identical in color and shape and the same number on the same schedule have to be administered regardless of treatment assignment.

Trials involve select study populations and hence are not representative of the general population. In fact, there is no way to make them so because you cannot study those who do not come forward for study or those who do not consent to study.

The value in trials is in the relative truth they provide. If a treatment works in the people studied it is likely to work in the broader population. If the trial involved only men and the treatment tested worked and can be used on women, chances are that the treatment will also work on women.

The goal is to cast the net as broadly as possible when enrolling, if only for achieving the enrollment goal in the shortest possible time. The more restrictive enrollment the harder it is to enroll.

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Typically, trialists do subgroup analyses to determine if treatment effects differ across subgroups of persons enrolled. The analyses are done to determine whether it is reasonable to regard the treatment effect observed as homogeneous across subgroups. The reality is that it is difficult finding a main effect without any subgrouping. The chances of finding subgroup differences are slim to none.