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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Relative truth

All you can learn from trials is whether the test treatment is better, worse, or the same as the control treatment. Relative truth. If you want more you need to go to a higher authority.

The Achilles heel of trials is that they involve select study populations. Populations not representative of the general population and no way to know how they differ.

Select because you cannot study those who do not come forward for study or those who do not consent to study.

But knowing how a treatment works relative to another is invaluable, even if in obviously select study populations. The saving feature is randomization and the fact (assuming properly done and administered) treatment groups are comparable and, hence, if outcomes are different it is likely due to the fact that the study treatment works differently than the control treatment.

Generally, a treatment that works, works across a broader spectrum of people than tested. So if a trial in women, involving a condition common to men, finds the treatment tested to be superior to the control treatment, it is likely the treatment will also be useful in men with the same condition, even though no men were tested.

That is what the science of trials tells us, but that does not jibe with the politics of trials. The treatment may work in men, but it will be a hard sell since the public expects trials to cover the waterfront. Excuses as to why a trial did not include men will not play in Peoria.

But trials always involve exclusions, even if open to all comers. Most trials are done in adults. Typically children are not included unless the condition afflicts children. Pregnant women and women likely to become pregnant are usually excluded as also often the case with the “elderly”.

The usual story in trials open to all comers is to have more women than men and underrepresentation of minority groups. Absent concerted efforts to recruit African-Americans (often not successful) that group will be underrepresented relative to the general population, due perhaps in part to distrust of the medical establishment dating back to the Tuskegee Syphilis Trials.

The usual approach to investigating whether treatment effects are homogeneous is by subgroup analyzses, for example in a trial involving both males and females by comparing treatment effects in males versus females.

Typically trials are not powered for subgroup analyses so power for subgroup comparisons is variable, and less than for the overall comparison. In general, believable subgroup differences are rare. That does not mean differences do not exist, but rather that power inadequate to find differences.

Obviously, demographic coverage is important in trials were results are applicable to the entire population, as in COVID-19 vaccine trials. The hope, because of the observation of greater COVID-19 mortality in minority groups, especially in African-Americans, is that those subgroups are overrepresented, but unlikely given minority representation in trials. That being so, be prepared for blizzards of complaints of how vaccine trials failed to cover the waterfront with the numbers desired.