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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: A new name for an old design strategy

As an aging dictionary writer I hear terms relevant to trials, but foreign to me. Though I doubt I have energy for a 3rd edition of my dictionary, I make mental notes just in case.

A term in the vernacular now is *platform trial*. For a time I chalked it up to a new design that had passed me by, but curiosity got the best of me, so I did what everyone else does, Googled, and came across a 2016 publication in **Clinical Trials** by Saville and Berry entitled: *Efficiencies of platform clinical trials: A vision of the future* and a definition of platform trial:

> *A clinical trial with a single master protocol in which multiple treatments are evaluated simultaneously*.

It dawned on me then that my first two trials, decades ago, were platform trials: University Group Diabetes Program: UGDP (1960-78) and Coronary Drug Project: CDP (1966-1976); https://jhuccs1.us/clm/PDFs/UGDPLind.pdf; https://jhuccs1.us/clm/PDFs/UGDPTrib_10Jul2015.pdf; https://jhuccs1.us/clm/PDFs/CDPBlog.pdf

The UGDP involved four test treatments and two placebos for treatment of people with type-2 diabetes. The CDP involved five test treatments and one placebo for treatment of people with prior histories of MIs. The UGDP had 12 clinics, the CDP had 55, and both had master protocols.

The authors write "*Adaptive platform designs offer flexible features such as dropping treatments for futility, declaring one or more treatments superior, or adding new treatments to be tested during the course of a trial*." We dropped two treatments in the UGDP for futility and added one (and dropped it later because of safety concerns). We failed to find a superior treatment.

We dropped three treatments in the CDP for futility. The other two treatments limped to the finish line without distinction.

Indeed, there are efficiencies testing multiple treatments in the same trial, but *A vision of the future*? Not likely.

Multi-treatment trials are not easy to mount or do and involve dosing and administration compromises not necessary in trials involving just one study treatment. Drug companies are loathe to submit products for head-to-head comparisons with competitor products. Life was easier in the UGDP and CDP because the drugs used were approved for marketing.

The first problem is getting study drugs. If the drugs are licensed they can be purchased, but getting matching placebos is another story. Drugs purchased will have markings imprinted by the manufacturer. It is illegal to make or dispense look alike pills with similar markings as placebos.

The solution in the UGDP was to have manufacturers donate unmarked drugs and like looking placebos.

The problem was solved in the CDP by purchasing drug in powder form and having a central pharmacy pack product and placebo in like-looking opaque capsules. A single placebo design meant that everybody had to take the same number of capsules, even if required amounts of drug could be delivered with fewer capsules.

The number of capsules per person was driven by the drug requiring the largest volume for administration – nicotinic acid; nine capsules per day; three morning, noon, and night.

It also meant everyone had be on the same pill schedule. The niacin treatment, because of "flushing" caused by the drug, had to be increased in steps over a three month period to reduce flushing. That meant everybody in the trial had to be stepped the same way to preserve masking.

The dosing problem was avoided in the UGDP by use of different placebos for the two orally administered drug with their own dosing schedules.