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12 May 2021

Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Advances in trials

The first modern day trial took place on the HMS Salisbury at sea in 1747. The trial was done by James Lind and involved 12 sailors with scurvy; six treatment groups and two sailors per treatment group.

The question that prompts this note is from my clinical trials daughter Jill, "What would you list as advances in clinical trials over your lifetime?".

The question set me thinking. If you were asked the question, what would you list?

I wish I could say that trials have gotten larger with harder outcomes over my lifetime, but I would be wrong. There is no evidence to indicate that is the case. If anything they are getting smaller, shorter term, with softer outcomes.

I also wish I could say that investigators have an expanding role in the way trials are designed and conducted, but again, I would be wrong. The trend is in the other direction.

My first trial was done using an IBM 1620, large enough to fill my living room, with less computing power than my cell phone. But rising tides raises all boats. Advances in data processing, important as they may be, are not unique to trials.

Also important but not unique to trials is the National Library of Medicine. No doubt, one of the greatest gifts to humankind.

Before the advent of MEDLARS® (**MED**ical **L**iterature **A**nalysis and **R**etrieval **S**ystem) and MEDLINE (the online counterpart to MEDLARS®) in the mid 1960s, finding publications was tedious and getting your hands on them required trips to the "stacks" of medical libraries.

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My list in response to my daughter's question follows

Nuremberg War Code

The Code is a document consisting of 597 words and 10 points generated during the Nazi war crimes trials. It spells out principles to be followed when researching on human beings. The first of the 10 points is that voluntary consent for participation is absolutely essential.

Indeed!

Being able to research on human beings is a privilege, not a right, granted by a trusting public. We would not be able to do what we do without public trust.

Interestingly, it took about 20 years before consents were required by the NIH; memo from the Surgeon General, dated 8 February 1966, informing recipients of NIH funding that informed consents would be required as conditions for funding henceforth.

IRBs

Established in 1974 by a U.S. Code of Federal Regulations. A mixed blessing because of the added layers of bureaucracy and added time required to get projects funded and started. The positive is the amount of time and attention IRBs devote to consents and how they are obtained. But as stated in the last paragraph on consents (point 1) in the War Code:

> *The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.*

Randomization

Ronald Fisher was the first to use randomization for treatment assignment. In his case, in agricultural experiments; described in *Studies in crop variation: II. The manurial response of different potato varieties*. J Agric Sci **1923**; 13:311-320. Soon randomization for treatment assignment was used in clinical trials.

Prior to randomization, assignments were based on day of the week, coin flips, or contained in sealed envelopes to be opened in order as numbered. The trouble with all those systems is that they depend on persons following the assignment recipe. If you have done any cooking, you know how difficult that is. The advantage to formal randomization schemes is that they provide indelible audit trails for documenting assignments.

Double masking (aka double blinding)

Single masking is done to keep study subjects from knowing the treatment they receive. Double masking is done to keep study subjects and investigators in the dark to treatments being administered. Single masked treatment assignments were introduced in the early 1900s. Double masking came much later.

The importance of masking as a bias protection is a function of the outcome measure. The more subjective the measure the greater the importance of masking. The harder more objective the outcome the less the importance.

Double masking has become the equivalent of the Good Housekeeping Seal of Approval. If a trial is not double masked it is viewed as “deficient”.

The downside of double masking is what it does to communications. It precludes communications with clinical investigators about treatment assignment and outcomes and diminishes their investigator role in trials.

Registration of trials

The FDA Modernization Act of 1997 required that the NIH, via the NLM, create a registry of trials. The act gave rise to ClinicalTrials.gov, launched 2000. There are now (1 May 2021) 376,046 studies in the registry; 292,984 trials (interventional studies).

Prior to registration there was no viable way of identifying trials except via the published literature – an obviously biased sample since only a small fraction of trials are published.

The registry was the only one until the WHO opened its registration platform consisting of 16 regional registries, accounting for about 30% of all registered trials. The registries should be combined so we have a single universal registry.

DSMBs

Data Safety Monitoring Boards, aka by various other names. Broadly, boards appointed by study sponsors or jointly by sponsors and study leaders, commissioned to review interim results during trials to made recommendations as to whether trials should continue unaltered.

The National Heart Institute funded a number of large multicenter trials in the 1960s, 70s, and 80s. Its leadership recognized the complexities in organizing and monitoring such trials. Pursuant to the point, it commissioned a panel to address issues in organization and monitoring such trials. The official name of the panel was *Heart Special Project Committee to the National Advisory Heart Council* but unofficially came to be known as the "Greenberg Report", after its chair. One of its recommendations was for monitoring bodies independent of investigator groups. The Coronary Drug Project was the first NIH trial monitored under the structure proposed in the Greenberg Report.

The tendency is for more separation and independence from investigator groups depriving DSMBs of what investigators bring to the table in monitoring and knowledge of the trial. That separation and masking reduces investigators to data collectors – an unfortunate trend.

CONSORT

The **Con**solidated **S**tandards **o**f **R**eporting **T**rials is an aid for reporting parallel group randomized trials. There have been various versions of CONSORT, the most recent was published in 2010. It consists of a 25-item checklist and a diagram for displaying counts of persons as they the progress through trials.

The motivation for CONSORT was to provide an aid to authors of publications to improve the quality of publications. The pièce de résistance of CONSORT is the schematic diagram designed for users to provide counts of study subjects as they proceed through the trial, starting with people screened for enrollment. The schematic is required by most journals.

Posted results

The Food and Drug Administration Amendments Act of 2007 (FDAAA) included the requirement that investigators post results of trials covered under FDA regulations on ClinicalTrials.gov within one year of completion; ultimately requirement extended to all trials. Failure to comply carries provisions for heavy fines. The requirement is to post without comment (likely a sop to journals concerned about copyright protections).

The requirement is still a work in progress. So far only about 1/3rd of completed trials have posted results.

Obviously posting is a poor substitute to publication, but better than nothing.

Meta analysis

The term, meta analysis, was coined by Gene Glass in his presidential address to the American Educational Research Association in 1972. He used the term to denote statistical synthesis of results of similar studies (**Glass** GV: Primary, secondary and meta-analysis of research. Educ Res **1976**; 5:3-8).

Trialists and meta-analysts get along about as well as robins and blue jays. A fair number of my rants posted to my blog site are about meta analysts, no doubt due to the perception that trialists have a duty to provide data for meta analysts when trials are finished.

But even a curmudgeon like me recognizes the importance of meta analysis to inform the public of results of like trials to provide global conclusions regarding treatments.