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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: The Coronary Drug Project revisited

The Coronary Drug Project was a secondary prevention trial born of an "epidemic" of sudden deaths in men in the prime of life in the 1960s. The CV death rates for men in their 40's and 50's were about four times those for similarly aged females. (The male-female differential remains, but CV deaths have fallen dramatically for both gender groups since the 1960s.)

Over its life, its investigators produced dozens of publications starting in 1967 and ending 1991. (See ClinicalTrials.gov NCT00000482 and NCT00000483 for list of publications.)

We were six years into the University Group Diabetes Program when the CDP started. I am not sure how the trial came to be called the Coronary Drug Project. The name is short and sweet. "Coronary" tells you what the trial is focused on and "drug" tells you the nature of the treatments to be tested. The only deficiency is that "project" is nondescript. If we were starting today I would argue for Coronary Drug Trial, CDT, but a rose by any other name would still smell as sweet.

The CDP was investigator-initiated with a lot of help from the National Heart and Lung Institute (now the National Heart, Lung, and Blood Institute). It took about three years to get the study funded. Just as we thought we had the go ahead, LBJ put a hold on funding. We needed help from Mary Lasker to get it unstuck.

Mary Woodward Lasker (1900 – 1994) was a philanthropist health activist. She and her husband founded the Albert and Mary Lasker Foundation in 1942 to promote health-related causes. She played major roles in promoting and expanding the NIH budget from $2.4 million in 1945 to $5.5 billion in 1985. Mary Lasker was an LBJ supporter because of their common interest in civil rights. Clearly she and the Johnson's were on first name basis judging from frequent mentions of Mary Lasker in Lady Bird's "A White House Diary".

The study started with five clinics: Albert Einstein Medical Center, Philadelphia; Mayo Clinic, Rochester; Presbyterian St Luke's Hospital, Chicago: United States Public Health Service Hospital, Staten Island; and University of Southern California, Los Angeles. Eventually the number was expanded to 53 clinical centers (actually 55 but two clinics withdrew soon after coming in).

Jessie Marmorston ran the University of Southern California clinic. Her husband was a movie producer, best known for the Unsinkable Molly Brown. After having observed me in meetings a few times she wanted me to take a screen test the next time I was in LA. She renewed the offer several times.

Who knows? If I had accepted I might have had a career in movies. Thank you, but no thank you.

The aims of the CDP were:
(1): To evaluate the efficacy of several lipid influencing drugs in prevention of coronary heart disease;
(2): To obtain information on the natural history and clinical course of coronary heart disease; and
(3): To develop methodology for the design and conduct of large long-term multicenter clinical trials.

The study, in addition to the aforementioned clinics, involved a coordinating center (Baltimore), central laboratory (Atlanta), ECG reading center (Minneapolis), drug procurement and distribution center (Perry Point, Md), and National Heart and Lung Institute medical liaison office. The coordinating center was headed by Chris Klimt with me 2nd in command.

The trial was designed to detect a five year mortality difference between a treatment group and the placebo-assigned group with a type I error of 0.01 and a type II error of 0.05, assuming a five year mortality in the placebo-assigned group of 0.30 and a 30% five year dropout rate. (The actual mortality rate was closer to 0.20 suggesting people enrolled where in better shape than the general population on which the estimate was based. No surprise.)

Enrollment was limited to males, aged 30 - 64, with prior histories of MIs. Randomization was by clinic and by risk group (two: Men having had a single uncomplicated MI and men having had two or more MIs or having had a single complicated MI).

Persons were randomized to:
ESG1: Mixed conjugated equine estrogen (Premarin); 2.5 mg / day,
ESG2: Mixed conjugated equine estrogen (Premarin); 5.0 mg / day,
CPIB: Ethyl chlorophenoxyisobutyrate; colfibrate (Atromid-S); 1.8 g / day,
DT-4: Dextrothyroxine (Choloxin); 6.0 mg / day,
NICA: Nicotinic acid; 3.0 g / day,
or
PLBO: Lactose placebo; 3.8 g / day.

Randomizations were issued by the coordinating center after a person was determined to be eligible and consented to enrollment. Randomization was by clinic and risk group and in blocks of 30 with four persons assigned to each of the five drug treatments and ten assigned to the placebo treatment.

The trial was double-masked, meaning neither the persons enrolled nor persons in study clinics knew what persons were receiving. To accomplish the masking it was necessary to place the different medicines in opaque capsules to mask taste and appearances.

People enrolled started on three capsules a day (morning, noon, and night); increased to six capsules per day at the start of the 2nd month of followup; and increased to nine capsules per day at the start of the 3rd month of followup, and maintained at that level thereafter.

The stepwise increase was due to the need to reduce flushing that would have been caused by nicotinic acid if people had started straightaway on nine capsules per day. The nine capsules per day were due to the volume of drug required with nicotinic acid.

Enrollment started March 1966 and ended October 1969. Data collection ended August 1974. The numbers enrolled by treatment group were:

ESG1	1,101
ESG2	1,119
CPIB	1,103
DT-4	1,110
NICA	1,119
PLBO	2,789
Total	8,341

The reason for having 2.5 as many people in the placebo-assigned group as in any of the five drug-assigned groups was because of the need for greater precision of the mortality estimate in the placebo-assigned group than in any of the five drug-assigned groups because the placebo-assigned group was involved in each of the five drug-assigned comparisons.

Of the five drug treatments, only two made it to the end, CPIB and NICA.

Three, ESG2, DT-4, and ESG1, were stopped early because of ill effects.

ESG2 was stopped in 1970 because of an excess number of nonfatal cardiovascular events and lack of evidence of efficacy with respect to mortality.

DT-4 was stopped in late 1971 because of excess mortality.

ESG1 was stopped in 1973 due to excess incidence of thromboembolism and excess mortality from cancer.

The results for the two treatments that made it to the end, CPIB and NICA, published in 1975, were less than overwhelming. The were about like placebo in regard to mortality.

I guess Matthew 22:14 “Many are called, but few are chosen” also applies to treatments in trials.

The trial was of the “publish first, present later” philosophy, meaning that all four treatment results papers were published before there were any presentations of results at scientific meetings.

Jeremiah (Jerry) Stamler was chair of the CDP. He grew up in New York City. He moved to Chicago in 1947 to work in a cardiovascular research laboratory under Louis Katz. During the CDP he was working for the Chicago Board of Health with offices in the Chicago Civic Center.

Stamler was a child of the Great Depression. I was reminded of that one Sunday afternoon in his office. We were writing letters about what I do not recall that we wanted to mail that day.

When the letters were ready, Jerry started searching for stamps, drawer by drawer. I joined him in pulling out drawers and eventually I found air mail stamps.

People reading this now will not know what I am talking about, but then, if you wanted letters to move faster you posted them with air mail stamps. The only catch was that the stamps were considerably more expensive than ordinary stamps.

“Hey Jerry. Here use these.”

“They are air mail stamps!”

“So. They will work.”

“I can’t use them.”

“Why not?”

“You don’t understand.”

“What’s to understand?”

“I am a child of the depression. There is no way I can bring myself to use an air mail stamp when a regular stamp will do.”

So the letters did not get mailed until the next day with regular stamps.

One day early in 1969 I learned that Jerry had been subpoenaed to appear before the House Committee Un-American Activities for hearings to be held in Chicago later that year. Stamler was willing to appear provided he could be accompanied by legal counsel. The Committee refused, Stamler refused the summons, and the Committee cited him for contempt. (The Committee, in an effort to reinvent itself, was renamed in 1969 the Internal Security Committee).

The legal wrangling went on for the better part of three years to a standoff. The Committee, due in part to Stamler, was formally dissolved on 14 January 1975, opening day of the 94th Congress.

It is not every day you get to work with someone cited for contempt of Congress who does in a House Committee!

A lot of what I know about organization of working groups in trials, I learned from Jerry. He was like a maestro conducting an orchestra when running meetings.

A dubious claim to fame is that the CDP was the beginning of monitoring bodies apart from the investigator group.

Monitoring in the UGDP was done by the steering committee. During the UGDP, Tom Chalmers was the associate director of the NIH and Director of the NIH Clinical Center. Though he was not directly involved in the UGDP, he was an avid observer. He was critical of the fact that investigators involved in the trial also monitored results to decide if treatments should continue. He regarded investigator involvement in monitoring as constituting a conflict of interest because they may be reluctant to stop a treatment or the entire trial because they are funded by the trial.

The Data and Safety Monitoring Committee in the CDP was about an even mix of persons internal and external to the CDP. The membership (as listed in the March 1973 American Heart Association Monograph detailing the design and methods of the trial) was:

Jeremiah Stamler (Co Chair)
Curtis L Meinert (Co Chair)
E Cowles Andrus
Henry Blackburn
Paul Canner
Thomas Chalmers
Jerome Cornfield
Fred Ederer (1968-1970)
William Friedwald
James H Gillette
Adrian Hainline (1968-1972)
Max Helperin
Gerald Klatskin
Christian R Klimt
Robert Levy
Dayton Miller
Elliot Newman
NHLI medical liasison officer

The committee met twice a year; more often if necessary. The committee saw unmasked data.

Recommendations to stop a treatment were passed to a policy board comprised of:

Robert W Wilkens (Chair)
Jacob E Bearman
Edwin Boyle
Louis Lasagna
William Smith
Max Helperin (ex officio)
Christian R Klimt (ex officio)
Jeremiah Stamler (ex officio)

William Zukel (ex officio)
Medical Liasison Officer (ex officio)

The board's function, among others, was to review recommendations from the monitoring body.

Over the course of the CDP, the board received three: Two to stop ESG1 and DT-4 and one to stop ESG2 in people in risk group 2. The board accepted the EGG1 and DT-4 as submitted, but extended the ESG2 recommendation to apply to all persons assigned to the treatment.

The practice of having a separate policy board to review recommendations coming from monitoring bodies has largely disappeared.

Eventually the NIH required monitoring bodies as stated in a release dated 10 June 1998:
It is the policy of the NIH that each Institute and Center (IC) should have a system for the appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data for all NIH-supported or conducted clinical trials. The establishment of the data safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. The data and safety monitoring functions and oversight of such activities are distinct from the requirement for study review and approval by an Institutional Review Board (IRB).

The trend now is for watertight separation of the monitoring body from study investigators. The reason is because of concerns that investigators having knowledge of data trends may bias data collection.

The trend to watertight separation is disconcerting because isolation of monitors from study investigators reduces the competency of the monitors to the extent that investigators, who collect the data, know the protocol and sand traps in data better than their external counterparts.

Even worse is the tendency to mask the monitors to treatment assignment, again because of the desire to avoid bias that may creep in if the committee knows treatment assignment. That practice is what led me to write, years back, "Masked monitoring, blind stupidity?" (NEJM 1998; 338:1381-82).

Lessons learned

1: The most important persons in trials are clinic coordinators. They know the protocol and data collection procedures better than their clinic directors.

2: There is no substitute for face-to-face interactions with the investigator group. The steering committee and investigator group in the CDP met every six months.

3: The value of site visiting was what clinics did to prepare for visits, not the visits themselves.

4: The key ingredient to success is competent leadership. We had that in the persons of Jerry Stamler (chair) and Ken Berge (vice chair).

Perspective

Sixty years after the CDP, a trial is still a trial. The same basic rules and principles apply. What has changed is how multicenter trials are initiated and how they are funded.

The CDP was investigator-initiated. Now the initiator role for large trials is usually vested in the funding agencies. Investigator initiation of a trial like the CDP is still possible, but initiation is not for the faint of heart. Now, often the better strategy is to wait for the NIH to initiate and then to apply as a center.

Another difference now is how multicenter trials are funded. The CDP was funded by individual grants issued by the NHLI. Today the approach would be to award the money to an agency that disburses the money to individual centers.

Postscript

We managed to avoid the brick bath we got in the UGDP for stopping tolbutamide, primarily because the medical community was not as invested in the treatments we tested as was the case with tolbutamide in the UGDP. (A large primary prevention trial of ischemic heart disease done by the WHO and published in the Lancet in 1980 showed 25% more deaths in the clofibrate-treatment group than in the control-assigned group.)

A decade or more after the CDP was finished it became a cause célèbre, cited by women's group as evidence of women being denied the benefits of trials by exclusion. The trials most frequently cited, in addition to the CDP, were the Physicians Health Study and the Multiple Risk Factor Intervention Trial. All three, male only.

An interesting twist because it was not that many years before that when people were complaining of being guinea pigs in trials.