JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
415 N. Washington Street, 2nd Floor
Baltimore, Maryland 21231

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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: My life as a trialist

Once you reach your dotage you start counting so you can figure out how you spent your life.

I am an accidental trialist. I did not wake up one morning on the farm and decide I wanted to be a trialist. Nor did I decide that was what I wanted to be when I was in gradual school. Trials found me when I got hitched up with Chris Klimt doing the University Group Diabetes Program (UGDP).

I grew up a Yankee fan (inherited from my father), so I am inclined to recount my history as a trialist in baseball terms.

An “at bat” corresponds to a treatment tested in a trial. For example, I had four “at bats” in the UGDP. One for each of the test treatments: Tolbutamide, phenformin, insulin fixed dose, and insulin as needed to control blood sugar.

I had 26 at bats with the 12 trials below. All 12 trials were NIH-funded, randomized, and multicenter except one, the Chemoprevention for Barrett's Esophagus Trial (CBET). The outcome for any given at bat is:

Strike out (K): Test treatment stopped early because of bad effects
Base on balls (BB): Test treatment stopped because of futility or slow recruitment
Pop out (PO): Test treatment not better or worse than the comparison treatment
Hit (H): Test treatment better than the comparison treatment

I struck out 7 times, popped out 10 times, and got 9 hits for a batting average of 346. With that average I have only one chance in three of having a winner. What the record tells me is that I and the people I run with are not very good at picking winners or that winners are hard to come by.

University Group Diabetes Program (UGDP)

Purpose: To determine if standard treatments for type-2 diabetics can reduce the risk of morbidity caused by the disease
Test treatments: 4: tolbutamide, phenformin, insulin fixed dose, insulin dose as needed for blood sugar control
No. enrolled: 1,027
Start-finish: 1961--1975
Conclusion: Tobutamide and phenformin treatments stopped early because of ill-effects; insulin treatments continued to end but results not markedly different from placebo assigned group.
Box score. . . . . K, K, PO, PO

Coronary Drug Project (CDP)

Purpose: To determine if mortality rates in men with prior histories of MIs could be reduced with treatment

Test treatments: 5: estrogen (2.5mg/day), estrogen (5.0mg/day), CPIB, (1.8g/day), dextrothyroxine (6.0mg/day), nicotinic acid (3.0g/day)

No. enrolled: 8,341

Start-finish: 1966–1975

Conclusion: The two estrogen and the dextrothyoxine treatment groups were stopped early because of ill-effects; CPIB and nicotinic acid continued to end but results not markedly different form placebo assigned group

Box score. . . . . K, K, K, PO, PO

Hypertension Prevention Trials (HPT)

Purpose: To determine if persons with blood pressures of 78 to 89 mm Hg on entry could be kept from becoming hypertensive over a three year period of dietary counseling

Test treatments: 4: reduced calories, reduced sodium, reduced sodium and calories, and reduced sodium and increased potassium

No. enrolled: 841

Start-finish: Jan 1983–Jan 1990

Conclusion: All four dietary counseling treatment groups experienced fewer hypertensive events; significantly fewer occurred in the sodium groups. The beneficial effects on blood pressure achieved in this trial have implications for the prevention of cardiovascular disease through dietary reduction of calories and sodium. (Arch Intern Med. 1990;150:153-162)

Box score. . . . . H, H, H, H

Glaucoma Laser Trial (GLT)

Purpose: To assess the efficacy and safety of argon laser trabeculoplasty as an alternative to treatment with topical medication for controlling intraocular pressure in patients with newly diagnosed Glaucoma

Test treatments: 1: Laser treatment for high intraocular eye pressure

No. enrolled: 271

Start-finish: Jan 1984–Nov 1990

Conclusion: After 2 years of follow-up, intra ocular pressure was controlled in 70% of eyes assigned to laser compared to 30% of eyes treated with timolol. There were no major differences between the two treatment approaches with respect to changes in visual acuity or visual field over the 2 years of follow-up. (Ophthalmology 1990; 97: 1403-1413)

Box score. . . . . H

Foscarnet-Ganciclovir CMV Retinitis Trial (FGCRT)

Purpose: To compare ganciclovir with foscarnet in the treatment of cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome (AIDS)

Test treatments: Ganciclovir

No. enrolled: 240

Start-finish: Mar 1990–Oct 1991

Conclusion: These results suggest that for patients with AIDS and cytomegalovirus retinitis, treatment with foscarnet offers a survival advantage over treatment with ganciclovir; trials stopped early because of mortality excess in ganciclovir treated group (NEJM 1992;326: 213-20)

Box score. . . . . K

CMV Retinitis Retreatment Trial (CRRT)
- Purpose: To determine the best therapeutic regimen, using currently approved drugs, for treatment of relapsed cytomegalovirus (CMV) retinitis
- Test treatments: 3: foscarnet group: induction with foscarnet followed by maintenance at a dosage of 120 mg/kg per day; ganciclovir group: induction with ganciclovir by maintenance at 10 mg/kg per day; continuation group: continuation of previous maintenance therapy plus induction with the other drug (either ganciclovir or foscarnet) followed by maintenance therapy with both ganciclovir and foscarnet
- No. enrolled: 279
- Start-finish: Dec 1992–Feb 1995
- Conclusion: For patients with AIDS and CMV retinitis whose retinitis has relapsed and who can tolerate both drugs, combination therapy appears to be the most effective therapy for controlling CMV retinitis. (Arch Ophthalmol 1996; 114:23-33)
- Box score. . . . . H, PO, PO

HPMPC Peripheral CMV Retinitis Trial (HPCRT)
- Purpose: To evaluate intravenous cidofovir as a treatment for CMV retinitis.
- Test treatments: 2: Intravenous cidofovir; high- or low-dose
- No. enrolled: 64
- Start-finish: Apr 1994–Mar 1996
- Conclusion: Intravenous cidofovir, high- or low-dose, effectively slowed the progression of CMV retinitis. (Ann Intern Med 1997;126:264-274
- Box score. . . . . H, H

Monoclonal Antibody CMV Retinitis Trial (MACRT)
- Purpose: To evaluate the efficacy and safety of an intravenous human monoclonal antibody to cytomegalovirus (CMV), MSL-109, as adjuvant treatment for CMV retinitis
- Test treatments: 1: MSL-109
- No. enrolled: 209
- Start-finish: Sep 1995–Nov 1996
- Conclusion: Intravenous MSL-109, 60 mg every 2 weeks, appeared to be ineffective adjuvant therapy for CMV retinitis. The mortality rate was higher in the MSL- 109-treated group, but the reasons for this difference remain uncertain. (Arch Ophthalmol 1997;115:1528-1536)
- Box score. . . . . K

Ganciclovir/Cidofovir CMV Retinitis Trial (GCCRT)
- Purpose: To compare the regimen of the ganciclovir implant plus oral ganciclovir to intravenous cidofovir for the treatment of cytomegalovirus retinitis
- Test treatments: 1: ganciclovir implant plus oral ganciclovir, 1 gm three times daily, or intravenous cidofovir, 5 mg/kg once weekly for two doses, followed by 5 mg/kg every other week.
- No. enrolled: 61
- Start-finish: May 1997–Apr 2000
- Conclusion: Data suggest the regimens of the ganciclovir implant plus oral ganciclovir and of intravenous cidofovir are similar for controlling cytomegalovirus retinitis and preventing visual loss. (Am J Ophthalmol 2001;131:457-467)
- Box score. . . . . PO

Chemoprevention for Barrett's Esophagus Trial (CBET)
- Purpose: Determine the safety and efficacy of celecoxib for regression of Barrett's dysplasia in patients with low or high-grade dysplasia of the esophagus
- Test treatments: 1: celecoxib
- No. enrolled: 100
- Start-finish: Jul 2000–Apr 2007
- Conclusion: Administration of 200 mg of celecoxib twice daily for 48 weeks of treatment does not appear to prevent progression of Barrett’s dysplasia to cancer. (J Natl Cancer Inst 2007;99: 545–57)
- Box score. . . . . PO

Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
Purpose: To evaluate the conventional NSAID naproxen sodium and the selective COX-2 inhibitor celecoxib for primary prevention of Alzheimer's dementia (AD)
Test treatments: 2: naproxen, celecoxib
No. enrolled: 2,528
Start-finish: Jan 2001–May 2007
Conclusion: Results do not support the hypothesis that celecoxib or naproxen prevent Alzheimer's dementia, at least within the early years after initiation of treatment. (Neurology 2007;68:1800-1808)
Box score. . . . . PO, PO

Citalopram for Agitation in Alzheimer's Disease Trial (CitAD)
Purpose: To evaluate the efficacy of citalopram for agitation in patients with Alzheimer's disease
Test treatments: 1: citalopram
No. enrolled: 186
Start-finish: Jul 2009–Feb 2014
Conclusion: The addition of citalopram compared with placebo significantly reduced agitation and caregiver distress (JAMA 2014:311(7):682-691. doi:10.1001/jama2014.93)
Box score. . . . . H