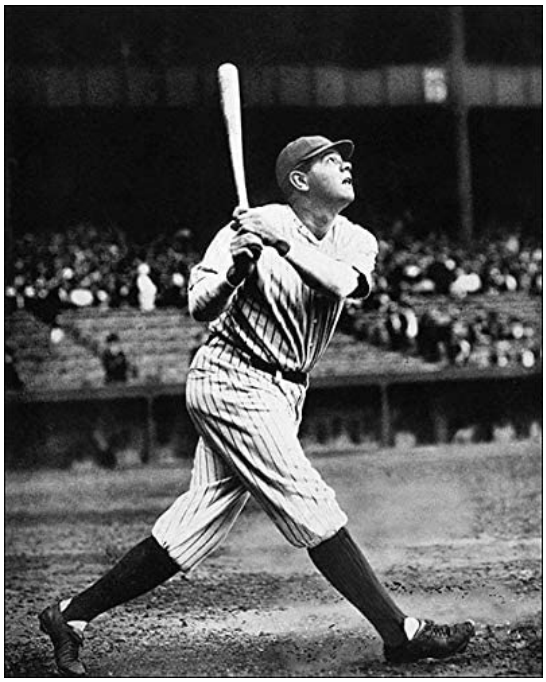

Life as a trialist

I am a tenured professor. I never told my parents that for fear they would think it was something bad. I also knew if I got beyond their concern, they would want to know what it meant and then I would be stumped.

Tenured professor. Job for life with one small caveat – that you raise your own salary.

Tenure is overrated. Basically all it means is that you cannot be fired except for moral turpitude, whatever that is. It does not mean you are entitled to a salary. So life as an "academic" means you had better be able to support yourself or you will be sent packing.

Life as a trialist

Academia is like farming. A farmer works his fields and plants his crops and if he does not get hailed out or froze out he is alright for another year. Otherwise it is food stamps.

In academia, the planting is done by submitting funding requests. If they are favorably reviewed they get funded. Otherwise it is hard times and the streets.

I am an accidental trialist. I did not wake up one morning and decide I wanted to be a trialist. Trials found me when I got hitched up with Chris Klimt doing the University Group Diabetes Program (UGDP).

My "record" in baseball terms for trials is summarized below.

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 ad lib.

I had 26 at bats for the 12 trials in which I had major roles.

The outcome for an at bat is:

Strike out (K): Test treatment stopped early because of bad effects
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; one chance in three of having a winner.

University Group Diabetes Program (UGDP)
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)
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: Two estrogen treatments and dextrothyoxine treatment stopped early because of ill-effects; CPIB and nicotinic acid continued to end but results not markedly different from placebo assigned group
Box score . . . . . K, K, K, PO, PO

Hypertension Prevention Trials (HPT)
Test treatments: 4: reduced calories, reduced sodium, reduced sodium and calories, reduced sodium and increased potassium
No. enrolled: 841
Start-finish: Jan 1983–Jan 1990
Conclusion: All four dietary counseling treatment groups had fewer hypertensive events; significantly fewer in reduced sodium treatment groups.
Box score . . . . . H, H, H, H

Glaucoma Laser Trial (GLT)
Test treatment: 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.
Box score . . . . . H

Foscarnet-Ganciclovir CMV Retinitis Trial (FGCRT)
Test treatments: 2: foscarnet, ganciclovir
No. enrolled: 240
Start-finish: Mar 1990–Oct 1991
Conclusion: Treatment with foscarnet had survival advantage over ganciclovir; trials stopped because of mortality excess in ganciclovir-treated group (NEJM 1992;326: 213-20)
Box score . . . . . H, K

CMV Retinitis Retreatment Trial (CRRT)
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 followed 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 whose retinitis has relapsed, combination therapy is the most effective for controlling CMV retinitis.
Box score . . . . . H, PO, PO

HPMPC Peripheral CMV Retinitis Trial (HPCRT)
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, slowed the progression of CMV retinitis.
Box score . . . . . H, H

Life as a trialist

Monoclonal Antibody CMV Retinitis Trial (MACRT)
Test treatments: 1: MSL-109
No. enrolled: 209
Start-finish: Sep 1995–Nov 1996
Conclusion: Stopped because of mortality in the MSL-109-treated group
Box score . . . . . K

Ganciclovir/Cidofovir CMV Retinitis Trial (GCCRT)
Test treatments: 1: ganciclovir implant plus oral ganciclovir, 1 gm three times daily, or intravenous cidofovir, 5 mg/kg once weekly for two weeks followed by 5 mg/kg every other week.
No. enrolled: 61
Start-finish: May 1997–Apr 2000
Conclusion: No difference
Box score . . . . . PO

Chemoprevention for Barrett's Esophagus Trial (CBET)
Test treatments: 1: celecoxib
No. enrolled: 100
Start-finish: Jul 2000–Apr 2007
Conclusion: Celecoxib ineffective in preventing progression of Barrett's dysplasia to cancer.
Box score . . . . . PO

Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
Test treatments: 2: naproxen, celecoxib
No. enrolled: 2,528
Start-finish: Jan 2001–May 2007
Conclusion: Results do not support hypothesis that celecoxib or naproxen prevent Alzheimer's dementia
Box score . . . . . PO, PO

Life as a trialist

Citalopram for Agitation in Alzheimer's Disease Trial (CitAD)
Test treatments: 1: citalopram
No. enrolled: 186
Start-finish: Jul 2009–Feb 2014
Conclusion: Citalopram reduced agitation
Box score . . . . . H

At Hopkins I live in the Center for Clinical Trials. I am surrounded by trials and trialists. The list below is trials and related studies completed or ongoing when the list was compiled (30 June 2014)

1 Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin Trial (APRON)
2 Asthma Early Intervention in Asthma Management (A+)
3 Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
4 Apathy in Dementia Methylphenidate Trial (ADMET)
5 Broccoli Sprout Extracts Trial (BEST)
6 Childhood Asthma Management Program (CAMP)
7 Chemoprevention for Barrett's Esophagus Trial (CBET)
8 Citalopram for Agitation in Alzheimer's Disease Trial (CitAD)
9 CMV Retinitis Retreatment Trial (CRRT)
10 Cysteamine Bitartrate Delayed-Release for the Treatment of NAFLD in Children (CyNCh)
11 Depression in Alzheimer's Disease Study-2 (DIADS-2)
12 Effect of Positive Airway Pressure on Reducing Airway Reactivity in Patients with Asthma (CPAP)
13 Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment Trial (FLINT)
14 Foscarnet-Ganciclovir CMV Retinitis Trial (FGCRT)
15 Ganciclovir/Cidofovir CMV Retinitis Trial (GCCRT)
16 Glaucoma Laser Trial (GLT)
17 HPMPC Peripheral CMV Retinitis Trial (HPCRT)
18 Hypertension Prevention Trial (HPT)
19 Infant Health and Development Program (IHDP)
20 Leukotriene or Corticosteroid or Corticosteroid-Salmeterol Trial (LOCCS)
21 Long-acting Beta Agonist Step-Down Study (LASST)

Life as a trialist

22 Long-term Oxygen Treatment Trial (LOTT)
23 Low Dose Theophylline Add-on Therapy in the Treatment of Asthma Trial (LODO)
24 Monoclonal Antibody CMV Retinitis Trial (MACRT)
25 Methacholine Bronchoprovocation Study (MeCIS)
26 Multicenter Uveitis Surgery Trial (MUST)
27 National Emphysema Treatment Trial (NETT)
28 Nortriptyline for idiopathic Gatroparesis Trial (NORIG)
29 Pioglitazone vs Vitamin E vs Placebo: NASH Trial (PIVENS)
30 Study of Acid Reflux and Asthma (SARA)
31 Study of Acid-Reflux in Childhood Asthma (SARCA)
32 Study of Asthma and Nasal Steroids (STAN)
33 Study of Inactivated Influenza Vaccine in Asthmatics (SIIVA)
34 Study of Soy Isoflavones in Asthma (SOYA)+
35 Tinnitus Retraining Therapy Trial (TRTT)+
36 Trial of Asthma Patient Education (TAPE)
37 Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC)
38 Wegener's Granulomatosis Etanercept Trial

* * * * *

I have crossed paths with 100s of people in my life as a trialist. Every trial, even a single center trial, involves dozens of people. Some trials, like the Coronary Drug Project, comprised of 55 clinics, involved hundreds of people.

The list includes a woman who wanted to get me into the movie business, a person cited for contempt of Congress, a Nobel peace prize winner, an adulterer, and a murderer.

Jessie Marmorston

Jessie Marmorston ran the University of Southern California clinic in Los Angeles in the Coronary Drug Project. Her husband was a movie producer, best known as the producer of the Unsinkable Molly Brown. After having observed me a few times in meetings she offered me a screen test the next time I was in LA. She renewed the offer several times.

Life as a trialist

Who knows what might have been if I had taken up the offer?

Jerry Stamler

Jerry Stamler was chair of the Coronary Drug Project. Stamler was a Chicago-based world renown cardiovascular epidemiologist.

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

Tom Chalmers

Tom Chalmers was a leading figure in trials.

He and one of my students, Kay Dickersin, wrote signature papers making publication bias a household term. For those who do not know and care to know (probably an empty set among readers of this treatise) publication bias is an inclination or tendency toward publication of results that support conclusions favoring a particular hypothesis or position.

I came to know Tom as an advocate of the UGDP after publication of the tolbutamide results and brickbats of criticism. He was the moving force behind creation of a special biometrics committee to review the trial.

Tom was a member of Doctors Without Borders, a France-based organization (Médecins Sans Frontières) best known for its projects in conflict zones and in countries affected by endemic diseases. The organization was awarded the Nobel Peace Price in 1999.

Over the years the two of us had many encounters. Perhaps the most pleasant was the opportunity to view On Golden Pond (a 1981 film staring Henry Fonda, his daughter Jane, and Katharine Hepburn) where it was filmed – in his cabin on a lake in New Hampshire.

Dirk Greineder

Dirk Greineder was an investigator in the Childhood Asthma Management Project from the Massachusetts clinic. He was German born and always reminded me of a soldier in Hitler's army. He was deliberate and thorough, good qualities for a researcher.

In November 1999 we learned his wife had been murdered. Later we learned that Dirk was the prime suspect and then came the trial and conviction.

Life as a trialist

Found guilty of 1st degree murder 29 June 2001

ABC News

A doctor accused of killing his wife to hide his secret trysts with prostitutes and his fascination with pornography was convicted today of first-degree murder and sentenced to life in prison with no chance of parole.

Prosecutors said allergist Dirk Greineder, 60, killed his wife Mabel Greineder, 58, on Oct. 31, 1999, while they were taking an early morning stroll in the woods near Morse's Pond, about a half-mile from their home in Wellesley, a wealthy suburb west of Boston.

The Norfolk County Superior Court jury reached its verdict after more than three days of deliberations.

Less than an hour later, the doctor received the mandatory sentence of life in prison without parole.

Greineder insisted he was not responsible for his wife's death, suggesting someone else attacked her. He told police he and Mabel separated during their walk after she wrenched her back, and that he later found her bloody, battered body. Her throat was slashed, and she had been bludgeoned with a hammer.

On the stand during his trial, Greineder admitted his wife had lost interest in sex and that he had paid two prostitutes for sex and had sex with two strangers. But, he tearfully told jurors, he still loved his wife and never considered asking for a divorce or killing her.

But prosecutors said they found Greineder's DNA on the weapons used to kill his wife. And photographs taken of Greineder shortly after her death showed blood on his clothes but not his hands. Greineder said he had gotten his wife's blood on him when he tried to move her body after finding her.