JOHNS HOPKINS
UNIVERSITY

Center for Clinical Trials

Department of Biostatistics
Department of Epidemiology
Department of International Health

Department of Medicine
Department of Ophthalmology
Oncology Center

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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Lessons from the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)

As a medical researcher, there is no better training than to be involved in multicenter trials. I have been involved in several over my career. Every trial teaches lessons or reinforces old ones.

Having just completed the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) and the ADAPT-Followup Study (ADAPT-FS), I am moved to catalog lessons learned from ADAPT before they are lost in the haze of the past.

My role in ADAPT was as director of the coordinating center. ADAPT involved six clinical centers located in Baltimore, Boston, Rochester (NY), Seattle, Sun City (AZ), and Tampa.

ADAPT was a primary prevention trial aimed at determining if anti-inflammatory drug treatment would prevent or delay the onset of Alzheimer's disease (AD) in people at risk for the disease. The design and methods of the trial are described in Alzheimer's Dement; Mar 2009; 5: 93-104.

The study enrolled 2,528 people. The two studies combined generated 17,300 person-years of followup, 26 publications, 46 steering committee meetings, 100s of conference calls, and enough frequent flier miles for a trip to the moon and back.

Below are lessons learned.

Lesson 1: Primary prevention trials are difficult!
Comment: They are difficult because you have to start with people who do not have the condition of interest and then you have to treat and follow to watch for development of the condition of interest. It is much easier to start with people who have the condition of interest and then treat and follow to see if they get better. Keeping healthy people taking drugs in the hope that they will be spared disease down the road requires acts of faith.

Lesson 2: It is difficult to justify continuing prevention trials in the absence of benefit
Comment: All drugs have potential for harm. That being said, how long do you continue drug treatment in the absence of any apparent benefit in preventing the condition of interest? The lack of even a hint of benefit after 4 years of treatment was what led to the decision to suspend treatment at end of 2004 when informed of the decision to stop celecoxib treatment in

an adenoma prevention trial (APC) on the morning of 17 December 2004 because of increased CV risks for people receiving the drug.

Lesson 3: Long-term trials are difficult to fund
Comment: ADAPT was investigator-initiated. Efforts to fund the trial started with a grant application submitted to the NIH in May 1997 and culminated, two submissions later, in funding in February 2000.

The period of time anticipated for enrollment was 12 months in the 1st and 2nd application and 18 months in the 3rd application (it took three years to achieve the enrollment goal) and the amount requested (5 yr totals) grew from $10,486,428 in the 1st application to $25,121,319 in the 3rd application.

An application for an additional five years of funding was submitted February 2004. The decision to suspend ten months later (see Lesson 5) rendered the application DOA. Funding after 2005 came from no cost extensions and supplemental funding from the NIH and a private foundation. Funding for ADAPT-FS came from the NIH via the American Recovery and Reinvestment Act (ARRA). Funding for the ADAPT coordinating center ended July 2013.

Lesson 4: Expect to be done in by the healthy person effect
Comment: Every trialist knows that people enrolled for study never have events at the rate planned. Invariably people enrolled are in better health than anticipated.

We selected people aged ≥70 having first degree relatives with age-related dementia. But even with risk concentration we ended up with event rates for AD well below those planned when the trial was designed. Mortality was predicted at 4/100 in year 1 with an 8% annual increment thereafter. The actual observed three year mortality rate was 1.27/100.

Lesson 5: Trials do not exist in vacuums
Comment: You would not know that from the monitoring structures for trials. To paraphrase Matthew 19:24 *It is easier for a camel to go through the eye of a needle than for data monitoring committees to share data*. Almost without fail, monitoring is done in watertight compartments with each trial viewed as the only trial of relevance. One can argue, with all the talk about data sharing, that a logical place to start is with exchange of data on safety and efficacy across like ongoing trials. One day I expect that to be the case but we are not there yet.

There was no data sharing (not to be confused with the data sharing referenced in Lesson 8) until I received a call at 7AM 17 December 2004 from Dr. Weiner of Pfizer informing me of their decision to stop the APC trial because of increased CV risks.

Lesson 6: Meta-analysis is like making sausage
Comment: The Cross Trial Safety Analysis (CTSA) was a collaborative meta-analysis spearheaded by Ernie Hawk of the National Cancer Institute. The effort involved principals from six placebo-controlled celecoxib trials (APC, PreSAP, MA27, ADAPT, CDME, and Celecoxib/Selenium). Together the trials represented a combined sample size of 7,950 (3,664 persons assigned to placebo and 4,286 persons assigned to celecoxib). The first meeting in relation to ADAPT participation took place on 20 June 2005. The manuscript summarizing results of the effort was published three years later (Circulation 2008; 117:2,104-2113) after

dozens of meetings with representatives of the six studies to agree on data included and excluded and for dealing with differences in data collection and protocols across trials.

Lesson 7: Adjudication is overrated
Comment: Adjudication, in the context of trials and observational studies, is a process involving a person or panel of persons tasked with reviewing safety events to provide a coding and classification independent of study investigators. Typically, adjudication is regarded as superior to counts of raw unadjudicated events because of variation in the way they are reported and because of the risk of bias in how events are codified or classified. An adjudication process was considered essential in CTSA because of differences in the way events were defined and reported across studies. But the reality, at least as far as ADAPT was concerned, the difference between raw and adjudicated counts was minimal.

Lesson 8: Data sharing before a study is finished pumps the well dry
Comment: The Clinical Trial Service Unit & Epidemiological Studies Unit of the University of Oxford organized an effort to harvest data from several celecoxib trials for a meta-analysis of outcome and safety data. We were asked to contribute ADAPT data in an e-mail dated 25 July 2008. The data set generated in relation to CTSA was sent 15 September 2009. A public use dataset was sent 19 May 2010. Results of the meta-analysis were published in Lancet May 2013 (Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials; www.thelancet.com; May 30, 2013; http://dx.doi.org/10.1016/S0140-6736(13)60900-9).

The downside of the data sharing while ADAPT was still ongoing was that it basically killed efforts in ADAPT to produce a comprehensive safety paper. No objection to the Oxford effort, but the world would have been better served by a paper from ADAPT investigators on safety.

Lesson 9: In academia, you cannot live by trials alone
Comment: The currency for promotion in academia is publication in peer-review scientific journals, ideally with the candidate for promotion as the sole author or first author. Multicenter trials like ADAPT take years to produce results and the authorship format is likely to be corporate. I fear I have done a disservice to young faculty by having them commit major portions of their time to trials leaving them shy of publications when they needed them for promotion.

Lesson 10: Once you say goodbye to patients it is hard to get them back
Comment: Anybody who has ever tried to restart followup once patients are separated from a trial knows how hard it is to restart. You need to reconnect and if you reconnect then you have to get new consents to proceed. There will be people you cannot find leaving you in the dark as whether they are alive or dead or developed AD in the interim. The gaps made for interesting analysis questions when trying to join the followup experiences in ADAPT to that in ADAPT-FS.

Lesson 11: Blind stupidity
Comment: I published "Masked data monitoring committees: Blind stupidity" in 1998 (NEJM 338:1,381-82). I did not expect to have to spend a year of my life arguing against masked monitoring in ADAPT. The problem in those battles, if it is you versus the chair of the monitoring committee or sponsor, you lose. The battle against masking was eventually won because I had ADAPT investigators on my side.

Lesson 12: Use patents
Comment: Until I got into ADAPT I had never heard of use patents only to discover two ADAPT investigators and the institution employing another one had use patents that would have generated royalties if celecoxib turned out to be a preventative for AD. Conflicts of interest come in various forms!

Lesson 13: It is over when the fat lady sings
Comment: Normally, in trials the fat lady sings when you run out of money, but in ADAPT it was over before that. The battle to get the safety results published was demoralizing as was the preoccupation with the need for adjudication. The PLoS paper (Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT); www.plosclinicats.org; Nov 2006) is not an adequate summary of the safety findings of ADAPT. There should have been a paper summarizing the safety results of ADAPT by ADAPT investigators.

Lesson 14: You cannot keep everything
Comment: As we prepare for another move (I have averaged one about every six years during my career) and moth-balling ADAPT, I was asked a few weeks back as to what I wanted done with e-mail files dated 14 December 2004 through 30 June 2005 stored at our Ann Street Office. I said I thought they should be tossed but that I should look at the material before tossing. A few days later I was dumbfounded to find ten 4" three ring binders on my desk representing the e-mails!

If I was an aspiring playwright I might be able to use the material to write a play, but I am just a farmer from Sleepy Eye, so I am tossing them!