

**Statement from the Steering Committee of the Alzheimer's
Disease Anti-inflammatory Prevention Trial (ADAPT)**
*for communication to the FDA Arthritis Advisory Committee
and the Drug Safety and Risk Management Advisory Committee*
18 February 2005

The Steering Committee of the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) welcomes the opportunity to present the rationale for its decision on 17 December 2004 to suspend the NSAID treatments in ADAPT. This presentation is important because there is much public misunderstanding about our decisions and their rationale.

The ADAPT Steering Committee is deeply committed to the safety of human subjects, even more so in the context of prevention trials where risks are typically not balanced by any promise of tangible near-term benefit. In this notable way, prevention trials differ from treatment trials whose participants may hope for relief of symptoms or improved outcomes in a condition already diagnosed. The risk-benefit balance in prevention trials is even further removed from a comparison of the benefits of a proven treatment with its acknowledged risks.

Because ADAPT has not quite completed the process of auditing and tabulating the trial's cardiovascular safety data on the date of suspension, we cannot today present the trial's safety results at the time of the decision to suspend. We defer that presentation to a peer-reviewed publication planned for the near future. For today, we note that, even within the risk-benefit calculus of a prevention trial, these data would not in themselves have led to a decision to suspend either treatment. In reality, those decisions were made in very unusual circumstances. They reflected events external to ADAPT that raised strong concerns about the practicalities of continuing the treatments.

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As the Advisory Committee probably knows, ADAPT is a randomized, double-masked, multicenter trial of celecoxib 200 mg b.i.d. or naproxen sodium 220 mg b.i.d. *vs.* placebo for the primary prevention of Alzheimer's dementia and for the prevention of age-related cognitive decline – in many instances a prodrome of Alzheimer's dementia. ADAPT also provides an opportunity to study the long-term safety of its treatments in a healthy elderly population. Eligibility criteria include an age of 70 yrs. or older at enrollment and a health history that excludes many of the known risk factors for adverse events with NSAID treatments (*e.g.*, we exclude those with pre-existing uncontrolled hypertension, anemia, or a history of gastro-intestinal bleeding, perforation or obstruction.)

To provide independent recommendations regarding continuation of the trial, the ADAPT Treatment Effects Monitoring Committee (TEMC) meets twice a year. In response to emerging concerns about cardiovascular risks with NSAIDs, membership of the TEMC was recently expanded to include Dr. Bruce Psaty, a physician with expertise in evaluation of cardiovascular risks in clinical trials. As an additional safeguard for participant safety, the ADAPT Study Officers (the Study Chair/PI, Director and Deputy Director of the Coordinating Center, and the NIA Project Officer) and consultants also conduct reviews of safety data at intervals between TEMC meetings. Amid the emerging controversy about the cardiovascular safety of selective COX-2 inhibitors, the ADAPT Study Officers had been relatively reassured by their periodic reviews of the celecoxib safety data. The Study Chair communicated this information in a telephone conversation on 15 October 2004 with Dr. Sharon Hertz at FDA.

As of 17 December 2004, the date of suspension of treatments and enrollment in ADAPT, we had enrolled 2,528 participants. Of these, 2,463 had been randomized before October 1, with some 20 months average duration of observations. These participants contributed 3,888 person-years of follow-up to analyses that were presented to the TEMC on December 10. Those analyses suggested a weak signal suggesting increased risks of cardiovascular and cerebrovascular events with *naproxen*. Reviewing the data, however, we understood well the TEMC's evident conclusion that this signal was not sufficiently compelling or definitive to warrant a recommendation to suspend the treatment or to otherwise alter the protocol.

Thus, the Officers were surprised on December 17 by announcements that two trials of celecoxib for the prevention of recurrent adenomatous colon polyps had been suspended citing increased cardiovascular risks with treatment in one of these studies, the Adenoma Prevention with Celecoxib (APC) trial. This news led to extensive discussion among the Steering Committee, centering on the following considerations:

1. One arm of the APC trial had used the same celecoxib dosing as ADAPT (200 mg b.i.d.), but over a longer period of time. News reports cited a relative risk of 2.5 for cardiac events in this arm of APC.¹ Although this risk was reported as only “marginally significant,” a greater cardiac risk signal was reported with the higher APC dosage of 400 mg b.i.d. Thus, we took seriously the possibility of harm over time to ADAPT participants receiving celecoxib. Especially in a prevention trial with no strong prospects of immediate benefit, we had strong misgivings about continuing celecoxib treatments.
2. Knowing almost nothing at the time about the particulars of the APC trial, and in light of the apparent lack of risk with celecoxib in the other polyp prevention trial, we might have discounted the APC data and continued celecoxib. To do so, however, we would clearly have needed the concurrence of the seven IRB’s that oversee ADAPT. These IRB’s began almost immediately to question us about implications of the APC results and seemed likely to question a decision to continue. Even if we had persuaded them to permit continuation of celecoxib using a revised consent process, we would surely be involved in lengthy discussions with these IRB’s. In the meantime, we would be unable to offer much explanation to our participants, thereby endangering the relationship of trust that is vital to the success of long term trials.
3. As is common in long-term trials, ADAPT was experiencing some difficulty with adherence to treatments. This difficulty grew following the withdrawal of rofecoxib, and we expected the announcement of the APC results to exaggerate the problem further with scores of participants stopping treatment, in effect “voting with their feet.” This would erode statistical power and increase the potential for bias in ADAPT.

Thus, even though the ADAPT safety data did not themselves warrant suspension of celecoxib treatments, there seemed little practical choice but to do so.

We next confronted the dilemma of what to do about naproxen and its placebo. As suggested above, we regarded the accumulated naproxen safety data as being somewhat more concerning than the celecoxib safety data, and yet they were also not compelling. Although some *post hoc* data composites barely reached statistical significance for naproxen vs. placebo, no single vascular event was clearly more frequent with naproxen *vs.* placebo. Furthermore, vascular risks were not expected with naproxen treatment. In fact, a substantial body of prior data had suggested that naproxen offers some cardiovascular *protection*.² This lack of prior expectation cast further doubt on the meaning of the naproxen data in ADAPT, which were vulnerable in any case to the problem of multiple comparisons.

We could therefore have attempted to revise ADAPT to a two-arm trial of naproxen *vs.* placebo, instructing our participants to stop taking their “white pills” (celecoxib and its placebo) but continue the “blue pills” (naproxen and its placebo). However, the dangers here were several:

1. Participants might end up getting confused and taking the “wrong” pills, and many would stop taking their treatments altogether.
2. We faced an ethical dilemma: the suspension of celecoxib and continuation of naproxen would have created the impression among participants, and among the general public, that celecoxib was risky but naproxen was “safe.” At least based on signals from the ADAPT data, this impression would have been misleading.
3. What would we then tell participants about the risks with naproxen as we led them through the inevitable process of revised consent necessitated by the protocol revision?
4. Would the multiplicity of IRB’s even allow us to follow this course?

Finally, there was another risk to consider. We began ADAPT expecting to see some increase with naproxen in gastro-intestinal (GI) bleeding and other events. Even though we attempted to reduce these excess GI risks by excluding participants with prominent risk factors other than age, the ADAPT data showed a notable increase in GI bleeding with naproxen *vs.* placebo.

Especially amid concerns that ADAPT was exposing its participants to potential risks that were immediate, while the trial's hoped-for benefits lay in the future, the totality of the above arguments led the Steering Committee to suspend both treatments and enrollment into ADAPT.

As noted above, we expect within a few weeks to submit a scientific paper for peer review and publication. The paper's focus will be on the process and rationale underlying the decision to suspend treatments and enrollment in ADAPT. Because those decisions did rely in some measure on the ADAPT safety data as of 10 December, the paper will also disclose some of those data.

We are also cooperating with ongoing efforts at NIH to investigate the cardiovascular and cerebrovascular risks of NSAIDs. In addition, the NIA and the ADAPT Steering Committee are committed to a further two years of additional safety monitoring of our participants.

In preparation for a later, more definitive discussion of the ADAPT safety data, we plan to re-visit a number of the adverse events to collect additional information, and then to submit all information (available now or later) to a process of expert adjudication. Depending on particulars, the latter process will take months. In the nearer term we concur with expert opinion that, having taken these widely publicized decisions, the Steering Committee must fulfill its obligation to disclose its reasons for doing so based upon the data available.³ At the same time, we are intent that our public presentation even of the current, "working" data must be at the highest attainable standards of accuracy.

References

1. Reported as hazard ratio 2.3, with 95% confidence interval (0.9 – 5.5) by Solomon SD, McMurray JJV, Pfeffer MA, et al., Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *New Engl J Med* 2005;352, available 15 February 2005 at <http://content.nejm.org/cgi/content/short/NEJMoa050405>
2. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risks of cardiovascular events and rofecoxib: a cumulative meta-analysis. *Lancet* 2004;364:2021-9.
3. DeMets DL, Pocock SJ, Julian DG, The agonizing negative trend in monitoring of clinical trials. *Lancet* 1999;354:1983-8.