DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

NOV 0 8 2002

Sidney M. Wolfe, M.D.
Public Citizen
1600 20th Street, N.W.
Washington, D.C. 20009-1001

Dear Dr. Wolfe:

Secretary Thompson asked me to reply to your recent letter expressing your concerns with the Alzheimer's Disease Anti-Inflammatory Trial (ADAPT) sponsored by the National Institute on Aging (NIA). You stated that new research on the class of drugs being tested invalidates the study's hypothesis and that informed consent documents are incomplete in disclosing important possible adverse effects to participants.

Let me assure you that the primary consideration in this or any clinical research is the safety and well-being of participants. In that regard, the Department carefully monitors the design and conduct of clinical trials that it supports. After a review of current activities of ADAPT, I am satisfied that the NIA is taking reasonable and necessary steps to ensure the conduct of a safe and scientifically sound clinical trial. At this time, the body of scientific evidence, the experience of patients in this trial, and the existing informed consent approach do not warrant halting this valuable Alzheimer's disease prevention study.

An enclosure to this letter, prepared by the NIA, offers a point-by-point response and details why the Department stands behind the scientific rationale for the study and assurances regarding the safety of participants in it. In summary:

- Scientific Hypothesis: It is true that recent research suggests that non-steroidal anti-inflammatory drugs (NSAIDs) other than those being tested in ADAPT might be used to reduce the amyloid plaques characteristic of Alzheimer's disease. This new research, however, does not invalidate the thinking that the anti-inflammatory action of the particular drugs being tested in ADAPT might prove effective against Alzheimer's disease. While the balance of evidence suggests that increased brain levels of beta amyloid are responsible for Alzheimer's disease, research has also shown that beta amyloid toxicity is accompanied by many other brain changes including inflammation,

oxidative stress, loss of connections between brain cells, and their dysfunction and death. At present, scientists cannot predict at what stage or stages in the disease process an intervention would be most effective yet have the fewest side effects. Each of these pathologies, therefore, is a legitimate target for therapeutic intervention, and there remains potential benefit in testing NSAIDS generally and naproxen and celecoxib, the two NSAIDs under study in ADAPT, specifically.

In addition to studies of naproxen and celecoxib, the NIA has funded a grant to carry out a Phase 1 clinical trial to test one of the new NSAID-related compounds that reduces beta amyloid levels in non-human models. The trial will test for safety and also for reduction in amyloid load in cerebrospinal fluid in older individuals. At an October 4, 2002, meeting of the ADAPT Steering Committee, ADAPT investigators discussed the issue of modifying the ADAPT trial by adding an arm for another NSAID. While the investigators and NIA do not find that option practical or feasible, the possibility of mounting a new prevention study with ibuprofen is now under discussion. The Data Safety Monitoring Board, at its upcoming biannual meeting, will also assess new studies in this area for their implications for ADAPT. These discussions reflect the commitment of the NIA and of the scientific community to continuously review science in this area.

- Informed Consent: At the time the study was initiated, we were confident that the consent form, as approved by institutional review boards at the six ADAPT sites, disclosed relevant potential adverse effects to participants based on current knowledge. In addition, we had systems in place and in use by ADAPT to evaluate the latest scientific findings and health and safety information. These are designed to ensure that participants are notified if necessary of new developments and that they can be monitored effectively throughout the course of the study. However, in light of the issues raised in your letter, we have requested that each study site's institutional review board review the 20-page ADAPT consent form.

Furthermore, the Food and Drug Administration (FDA) reviews all protocols submitted as part of a sponsor's Investigational New Drug application to determine whether the study can proceed. FDA reviews protocols to assure the safety and rights of subjects, and to assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety. In addition, FDA has the authority to place clinical trials on hold if scientific or safety concerns arise.

Alzheimer's disease affects as many as four million people in the U.S. As the population ages, the disease will affect millions more, including families and friends who care for loved ones whose memory and function are gone. After years of basic and epidemiological studies, a new

era in Alzheimer's research is under way as we move into testing clinically the strategies that science tells us could make a difference. I assure you that as these studies move forward, we will continue to engage in scientifically valid research with patient protection paramount.

I am sending a similar response to Drs. Barbehenn and Lurie.

Sincerely yours,

Ruth Kirschstein, M.D.
Deputy Director

Enclosure

NIH:NIA/OD:RHODES:pj:301-496-9265:9/12/02
Revised: NIH:NIA:VCahan:eo:61753:10/7/02
Revised:NIH/ES:klm:10/10/02
Revised:NIH/ES:TGill:10/11/02
Revised:OS/ES:LFishback:11/5/02
Official file located in NIH Director's files, Bldg 1, Rm B1-52
NIH Document #193450 (OS #090420020022)

The National Institute on Aging's ADAPT Trial

(Note: Numbers in brackets are references in Public Citizen letter. Numbers in parentheses are references listed in the response document)

Introduction

The National Institute on Aging (NIA) funds the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), a long-term clinical trial to determine whether commonly used non-steroidal anti-inflammatory drugs (NSAIDs) might prevent Alzheimer's disease (AD) in people at risk of serious age-related memory loss, dementia, or AD. The 7-year trial of naproxen and celecoxib is being conducted at six sites around the U.S., coordinated by Principal Investigator John Breitner, M.D., of the University of Washington School of Medicine and the Department of Veterans Affairs Puget Sound Health Care System.

On September 4, 2002, Secretary of Health and Human Services Tommy Thompson received a letter from Public Citizen raising questions about ADAPT and asking that the study be stopped, citing new research on NSAIDs and AD and issues in informed consent. The NIA is aware of emerging science in this area but at this time believes that the body of scientific evidence, the experience of patients in this trial, and the existing informed consent approach do not indicate that ADAPT should be summarily halted. The Institute, however, exercising its responsibility to ensure the protection of study participants, is addressing carefully and expeditiously issues raised by the Public Citizen correspondence.

While the balance of evidence suggests that increased brain levels of beta amyloid are responsible for AD, research has also shown that beta amyloid toxicity is accompanied by many other brain changes including inflammation, oxidative stress, loss of connections between brain cells, and their dysfunction and death. At present, scientists cannot predict at what stage or stages in the disease process an intervention would be most effective, yet have the fewest side effects. Each of these pathologies, therefore, is a legitimate target for therapeutic intervention.

The possibility that anti-inflammatory agents in particular might prevent the development of AD is suggested both by epidemiology research, where most, but not all, studies have shown that people who take NSAIDs may have a reduced risk of developing AD, as well as by studies showing that the brains of people with AD have an increased inflammatory response when compared with normal individuals of the same age. It was initially hypothesized that these drugs affect development of AD through their anti-inflammatory activities. Most discussion has revolved around whether the anti-inflammation activity was more likely to be mediated by inhibition of one or the other of the 2 cyclooxygenase enzymes, COX-1 or COX-2. It was proposed that newly developed anti-inflammatory drugs with only COX-2-inhibitory activity might delay AD's onset with fewer gastrointestinal side effects than traditional NSAIDs. Therefore, it was decided to test both naproxen, which inhibits both COX-1 and COX-2, and celecoxib, which inhibits only COX-2, in the ADAPT trial.

Recent studies, however, cited by Public Citizen, do show that that some anti-inflammatory drugs may have modes of action in addition to their COX-1- and COX-2-inhibitory activities. For example, in a November 2001 report, quite high concentrations of certain anti-inflammatory drugs (ibuprofen, sulindac and indomethacin) but not others (naproxen, celecoxib and several others) inhibited the production of one particularly detrimental form of beta amyloid in tissue culture, and ibuprofen, but not naproxen, also inhibited production of this beta-amyloid in a transgenic mouse model of AD. [reference 1 in the Public Citizen letter]. In another report, an experimental NSAID, a flurbiprofen derivative, reduced amyloid plaques in a transgenic mouse model of AD much more effectively than ibuprofen. The effect of celecoxib was not statistically significant. (1) In another series of experiments, ibuprofen was shown to reduce plaque number in transgenic mice (2), but other compounds were not tested. Public Citizen's interpretation of these latest studies is misleading, however, failing to note that none of these results bears on the question of whether the anti-inflammatory action of NSAIDs might be protective against AD, over and above the effects of some of these drugs on reducing amyloid. It should be noted that effects of NSAIDs on amyloid reduction have not been demonstrated in humans.

Other hypothesized mechanisms for a protective effect of NSAIDs against AD include their antiplatelet effects, reduction of glutamate-related excitotoxicity, and inhibition of free radical production (3)

Laboratory research and epidemiological studies in humans can identify mechanisms and associations that suggest a drug might have a protective effect. However, clinical trials are the only way to rigorously test the hypotheses generated from test tube, animal and epidemiological studies. Even in clinical trials, different drugs may be effective by working at different stages of a disease. Many scientists think it possible that some drugs may be effective only at early stages of AD, when cell death has not occurred and when plaques are more easily removed (the stage modeled in all the transgenic mouse models so far), but that these same drugs might not be effective in later stages of AD. This is the rationale for continuing to fund the ADAPT prevention trial on NSAIDs, where people are being treated when they are still cognitively intact, despite the fact that a recent trial of anti-inflammatories on persons who already have AD was negative.

NIA and consulting national and international scientists conclude that there is currently no evidence that the treatments being tested in ADAPT are of an unacceptable risk or seriousness relative to possible benefits. At the same time, studies of underlying biological mechanisms are of interest and warrant further analysis. The NIH will continue to fund these important studies on alternative mechanisms and their possible clinical relevance. In addition:

- Important issues of scientific merit, study design, and patient safety, including those raised in the letter received by the Secretary, will be addressed expeditiously.

- The recent meeting of the ADAPT Steering Committee has addressed these issues as will the planned meeting of the Data Safety Monitoring Board (DSMB), as is NIA. Each study site's IRB has also reviewed the consent form in light of the Public Citizen letter.

- We will always be ready to make appropriate decisions on whether the accumulating evidence is reason enough to modify or to stop the study, as we do for all the clinical trials that we fund.

References for Introduction.

(1) Jantzen PT, Connor KE, DiCarlo et al.: Microglial activation and beta-amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. *J. Neurosci.* 22: 2246-2254, 2002.

(2) Lim GP, Yang F, Chu T et al.: Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J. Neurosci.* 20: 5709-5714, 2000.

(3) Zandi PP, Anthony JC, Hayden KM, et al.: Reduced incidence of AD with NSAID but not H2 receptor antagonists. *Neurology* 59:880-886; 2002.

Point-by-Point Comments

1. Issues relating to study hypothesis.

Page 2, 4th full paragraph: The NSAID hypothesis, however, has turned out to be more complicated than this, and it is now felt that the inflammatory response is secondary to amyloid deposition and not the cause of it [7].

As often happens in biological research, the NSAID hypothesis has indeed become increasingly complex, but the implications of this complexity remain to be determined. If the inflammatory response is secondary to amyloid deposition -- a question not yet resolved -- this finding would in no way invalidate the targeting of inflammation as a therapeutic or preventive strategy. Many drugs are currently being developed that may not directly affect amyloid deposition but yet may prevent some of the harmful effects of such deposition. In fact, the only drugs currently approved by the FDA for the treatment of AD were developed to inhibit cholinesterases, thus maintaining brain levels of the chemical messenger, acetylcholine.

Page 3, 1st full paragraph: This is because the effect of NSAIDs is "independent of their inhibition of cyclooxygenase." [8]

This direct quote from the last paragraph of [8] is taken out of its context. The full sentence reads: "However, it has been shown recently that some anti-inflammatory drugs may have direct effects on the cleavage of APP by gamma secretase, independent

of their inhibition of cyclooxygenase and other inflammatory mediators." The authors of [8] are not suggesting that there are no effects of anti-inflammatory drugs other than their effects on amyloid production. They are only saying that the effects of anti-inflammatory drugs on amyloid production are independent of cyclooxygenase.

Page 3, 1st full paragraph: The fact that only certain NSAIDs inhibit this activity explains the lack of a class effect [9].

As the evidence stands now, this statement is not correct. It is not yet proven that some but not other NSAIDs are ineffective against AD, nor that any such effect is because only certain NSAIDs inhibit this activity (amyloid formation). The NIH is currently funding much of the research to determine whether or not NSAIDs work on AD and, if so, the mechanism for this effect.

Page 3, 1st full paragraph: According to the investigators, the choice of celecoxib was "mostly because of pharmaceutical company support " [10]; similarly, the choice of naproxen was also based on "Support from pharmaceutical company", [11] while according to an NIA spokesperson, "we try to save money". [12].

At the time the ADAPT protocol was drafted, there was no reason to believe, based on either basic science or epidemiological studies, that in this Alzheimer's disease prevention trial any conventional NSAID (e.g., ibuprofen or naproxen) would have an advantage over any other, nor that any selective COX-2 inhibiting NSAID (e.g., celecoxib or rofecoxib) would have any preferential effect. In fact, the decision to develop a treatment arm for ADAPT using a selective COX-2 agent was not proposed originally by the investigators, but was added later at the suggestion of a peer review panel of distinguished scientists judging the merits of the grant application. The offer from some pharmaceutical companies to make available naproxen (as Aleve) and celecoxib (Celebrex), as well as matching placebo tablets or capsules, was seen as a substantial opportunity. Not only did this afford considerable cost savings to the trial, but it also resolved serious and considerable practical problems in developing a placebo for other compounds. For example, if the investigators had wanted to test ibuprofen, the dose would have been 400 mg twice a day. However, no 400 mg tablet or capsule is commercially available and no matching placebo would have been available. In order to do the study, 200 mg capsules of ibuprofen would have had to be over-encapsulated and a matching placebo would have had to be made, resulting in very large and difficult-to-swallow capsules, and two of these capsules would have had to be taken twice a day. It was strongly felt this would affect compliance, especially in such a long-term trial. Furthermore, the bioavailability of the ibuprofen in the over-encapsulated preparation would have had to be determined, and, if the trial did in fact show a reduction in AD risk with treatment, there would be no commercially available formulations for general use.

Over two dozen NSAIDs are available on world-wide markets with others under development. Some, such as sulindac and indomethicin have more severe side effects, including gastrointestinal bleeding and discomfort (indomethicin) (1) and severe exfoliative skin reactions (sulindac) (see drug label), than newer drugs and therefore are not frequently prescribed. Hence, epidemiological data for these drugs is sparse (2).

Page 3, 2nd full paragraph. Data from an observational human study showing a protective effect of NSAID use [13] were recently reanalyzed to show that the apparent protective effect was restricted to ibuprofen, indomethacin, and sulindac, but, again, did not include naproxen. [14].

The Rotterdam study data referred to above are not yet peer reviewed and were presented at a meeting in Stockholm in late July 2002 (3). The data, suggesting that ibuprofen, indomethacin and sulindac were protective while naproxen was not, were presented on a poster session at that meeting. As with other epidemiological studies, subdividing results into subcategories reduces the power to see effects because of a smaller number of cases in each sub-group. We have requested information about these new data from the investigators, but until we get this information, or until it has been published in peer-reviewed form, we cannot comment on the validity of their conclusions. In this regard, it might be possible to reanalyze data from many of the previously reported anti-inflammatory studies, both those with positive and those with negative results, to determine if there were any trends in the efficacy of different anti-inflammatory agents. The NIA will support such analysis through peer-reviewed mechanisms.

Page 3, 2nd full paragraph: A clinical trial of AD treatment, using rofecoxib (a different COX-2 inhibitor from celecoxib) and naproxen, was recently halted since neither NSAID showed any benefit in any of the endpoints. [15].

This statement is incorrect. The Alzheimer's Disease Cooperative Study (ADCS), a multi-site clinical trials consortium funded by the National Institute on Aging, initiated this treatment clinical trial to determine if either of these two NSAIDs would affect the progression of AD over a one year period in people who had the disease already. The trial initiated enrollment in December 1999 and the trial ended in December 2001. It was completed according to the schedule originally proposed in its protocol, not halted. The DSMB monitored safety data throughout the study, as in all cases. When the data from this completed study were analyzed, it was found that neither drug affected the progression of AD. It is important to note that the treatment efficacy of certain drugs for people with AD may be quite different from the effectiveness of these drugs in preventing or delaying the development of disease in people who are at risk but do not currently have symptoms. This is an important issue that NIA is addressing in a number of current and potential future trials for AD.

Page 4, 2nd full paragraph: The doses chosen are celecoxib, 200 mg twice a day and naproxen sodium, 220 mg twice a day. A summary of the study states that, "It is recognized that the doses of the trial's two treatments are not pharmacologically equivalent (the celecoxib dose being somewhat stronger)." [17].

The ADAPT investigators chose the dose of celecoxib in order to maximize the likelihood of effect in preventing AD by providing the highest dose compatible with safety concerns as understood at the time; therefore, the 400 mg/day dose was chosen. Safety concerns dictated the use of a lower dose in the case of naproxen. Also there were good data to suggest that low-dose conventional NSAIDs, such as naproxen, were at least as efficacious as high doses at reducing risk of AD (2,4), and there were good data to show reduced risk of adverse events with over-the-counter doses compared with

"standard" doses (5,6). Finally, it is important to point out that the study was not designed to compare celecoxib to naproxen but to compare each to the placebo to determine if either one or both could prevent cognitive decline or AD.

Page 4, 3rd full paragraph: The inflammatory premise is one about which there has been much debate, and although it received early support, appears to have been largely supplanted by more recent research [18].

Reference 18 presents evidence in support of the fact that development of drugs specifically inhibiting the enzymes that clip beta amyloid from its precursor will be a compelling strategy to prevent AD. This does not obviate the importance of pursuing other strategies such as that based on inhibiting inflammation. To address our mission in finding effective means to treat or prevent AD, it is imperative that we follow up on a number of different leads for AD prevention - not only drug interventions to prevent beta amyloid deposition but also interventions to modify other mechanisms such as those affecting other key processes involved in brain cell injury and death. Lifestyle changes that can protect against AD also must be pursued. Analogies exist in the demonstrated effectiveness of different approaches found to be effective against other diseases, such as heart disease and diabetes.

Page 4, 3rd full paragraph: In the current amyloid hypothesis, the inflammatory reaction is a secondary response, not the primary event [19].

Again, even if the inflammatory response is a secondary event, preventing it may lessen some of the negative consequences of amyloid formation. Moreover, it remains possible that inflammation contributes to a vicious cycle of events in the brain, including amyloid formation (7)

Page 4, 3rd full paragraph: Although some NSAIDs inhibit the gamma-secretase, the two chosen for the ADAPT trial (naproxen and celecoxib) have never been shown to have such activity. They showed no lowering of amyloid levels in model systems [20], no benefit in a population-based cohort study, [21] nor any benefit in a recent clinical trial of AD that used naproxen and rofecoxib, another COX-2 inhibitor. [22].

While it is true that naproxen and celecoxib "have never been shown to have this activity" there has only been one study, published in November 2001 (variously referenced in the letter as *1*, *9* and *20*), that shows ibuprofen, indomethacin and sulindac sulphide to have amyloid lowering effects in tissue culture while naproxen and celecoxib did not. This same study is the only one yet to show that of the two drugs tested in transgenic mice, naproxen did not lower beta amyloid 1-42 while ibuprofen did. Yet, the authors of this study clearly state in their discussion, "However, our results do not exclude the potential benefits of NSAIDs in reducing the inflammatory response in the Alzheimer's disease brain."

In a previous study, high dose ibuprofen was shown to significantly reduce amyloid pathology in transgenic mice (2). At the time this paper was published, the result was taken as evidence for a general effect of anti-inflammatories on AD pathology rather than as evidence that ibuprofen was acting through another mechanism. Preliminary evidence does suggest the importance of continued experiments in animal

models, and ongoing assessment and re-assessment of the scientific rationale underlying clinical trials of candidate interventions.

NIA has already funded a grant [P01 AG20206] to compare the efficacy of different NSAIDS and related compounds in animal and human studies and to carry out a Phase 1 clinical trial to test one of the new NSAID-related compounds that reduces beta amyloid levels in non-human models. The trial will test for safety and also for reduction in amyloid load in cerebrospinal fluid in older individuals. At the October 4, 2002, meeting of the ADAPT Steering Committee, the ADAPT investigators discussed the issue of modifying the current trial by adding an additional arm for another NSAID. While they did not find that option practical or feasible, they did discuss the possibility of mounting a new prevention study with ibuprofen, and information regarding this option will be considered further by the investigators over the next few months. As noted above, the state of this science is under continuous review and its implications will be assessed at the upcoming meeting of expert scientists as part of the DSMB process

References for hypothesis.

(1) Rogers J, Kirby LC, Hempelman SR et al.: Clinical trial of indomethicin in Alzheimer's disease. Neurology 43:1609-11; 1993.

(2) In t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, Breteler MMB, Stricker BHC: Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 345:1515-1521, 2001.

(3) Breteler MMB, In t' Veld BA, Hofman, A and Stricker B. A β-42 peptide lowering NSAIDs and Alzheimer's disease. *Neurobiol. Aging* 23: S286, 2002

(4) Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP, et al.: Anti-inflammatory drugs protect against Alzheimer's disease at low doses. *Arch Neurol* 57:1586-1591, 2000.

(5) Perez-Gutthann S, Garcia-Rodriguez LA, Raiford DS: Individual nonsteroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology* 8:18-24, 1996.

(6) Garcia-Rodriguez LA, Jick H: Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *The Lancet* 343: 769-772, 1994.

(7) Akiyama H, Barger S, Barnum S et al.: Inflammation and Alzheimer's Disease. *Neurobiol. Aging* 21: 383-421, 2000.

2. Issues relating to participants' informed consent.

One reason for halting the ADAPT study, Public Citizen charges, is that "patients are taking drugs without true informed consent." (Page 1 of letter, 1st paragraph) Calling the trial "unethical," the letter goes on to specifically list adverse events associated with long-term use of NSAIDs and offers a comparison of the informed consent documents with the Warnings and Precautions sections in FDA-approved labels for celecoxib and naproxen.

As it does with any clinical trial, the NIA has closely monitored the ADAPT trial, along with institutional mechanisms set up to ensure informed consent and participant safety. In NIA's view, the investigators and institutional review boards at the six sites have disclosed relevant potential adverse effects to participants based on current knowledge. Further, systems have been in place and are in use to evaluate the latest research findings and health and safety information, and the NIA is confident that participants will be informed if necessary of new developments and that they can be monitored effectively throughout the course of the study.

The issues raised about informed consent are addressed below in a general description of ADAPT's informed consent documents and procedures and participant safety monitoring process. In addition, we include a point-by-point response to the letter's listing of potential adverse effects.

General description of informed consent and safety monitoring:

The safety of participants is paramount in all NIH studies. Before enrolling in any study, a participant must give his or her informed consent. That is, the participant must be informed in writing of all the potential risks and benefits that come from participation in the study. Informed consent documents and procedures must be approved by the Institutional Review Boards (IRBs) at each medical center where the study will be conducted; in the case of ADAPT, six independent institutions. Along with physicians and scientists, non-scientists and medical ethicists sit on IRBs to ensure that the risk/benefit information is accurately presented and conveyed in language that is understandable to people without scientific backgrounds. Each IRB is informed annually of the progress of a study, including safety issues.

Furthermore, the Food and Drug Administration (FDA) reviews all protocols submitted as part of a sponsor's Investigational New Drug application to determine whether the study can proceed. FDA reviews protocols to assure the safety and rights of subjects, and to assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drug's effectiveness and safety. (See CFR 312.22.) In addition, FDA has authority to place clinical trials on hold if scientific or safety concerns arise. (See CFR 312.23 for the regulatory criteria for a clinical hold.)

As is the procedure for other large NIH-funded clinical trials, the members of the DSMB and scientists at the NIH also review the informed consent documents and procedures and the safety monitoring plan. The DSMB for ADAPT consists of scientists and physicians who are experts in clinical trials, AD, and the drugs that are being used in the study. The voting members of the DSMB are also selected for the absence of any association or conflict of interest involving the institutions and scientists involved in ADAPT. Any serious side effects experienced by a study participant are reported to the FDA, the NIA, and to all study sites, which handle these reports according to their IRB's

requirements. The DSMB meets twice each year to review both safety information from the study, as well as any other scientific and medical information, such as newly reported side effects of drugs, that may bear on the safety of the study. DSMB membership also includes scientists from the NIA.

The Public Citizen letter has been distributed to IRBs at all study sites and the consent process and consent forms are being reviewed in light of its content. The principal investigator reported that some IRBs have suggested minor wording changes and all await the formal HHS response to the letter. In light of the letter, at the biannual Steering Committee meeting for ADAPT, held October 4, 2002, Committee members agreed that appropriate revisions to the consent documents could be submitted to the IRBs (see below).

DSMB members are also aware of the Public Citizen letter and will discuss it at their biannual meeting in November.

Adverse effects:

All drugs have side effects, some of which can cause "adverse events" ranging from discomfort and illness, to death. After the FDA approves a drug for marketing, any and all adverse events that were documented during clinical trials, whether or not they were likely to be related to the use of the drug or not, are noted in the label for the drug. (The same information is published in the Physicians' Desk Reference, which is available on the Internet now.) This is done because it is often impossible to assign causality to a problem in the presence of illness and other drugs and medical treatments. FDA-approved labels therefore, are exhaustive. They are designed for physicians and are both legal documents and marketing tools. In addition, they refer to a different population of patients and higher doses of drugs than those used in ADAPT.

Like many of today's thorough consent forms, that for ADAPT is extensive, consisting of 20 pages. The full FDA-approved labels for naproxen and celecoxib consist of an additional 30 pages of information that includes some dense and technical language. All relevant information contained in the FDA-approved label has already been included in the consent form, as judged by study IRBs . Supplying participants with the full FDA-approved labeling information therefore is not a standard or widely accepted practice for clinical trials.

Consent forms are not as comprehensive as a drug label, but are designed to present the potential risks and benefits of taking a drug in as clear language as possible. Whether the consent form is comprehensive enough is subjected to multiple layers of review, as delineated above. Trial participants are encouraged to ask questions and could certainly receive the drug labeling information on request. If and when potentially relevant new information becomes available concerning possible adverse effects of a drug, consideration is given to including this information as a revision of the informed consent document. Specific action being taken in this regard by the ADAPT study is described in detail below.

All information in the Contraindications, Warnings, and Precautions sections in FDA-approved labels should be considered in the safety monitoring of clinical trials. It was and continues to be considered for ADAPT, through oversight including that provided by IRBs and the DSMB, with NIA participation.

The consent form for ADAPT contains information on each of the adverse events described in these sections of the FDA-approved label, with the exception of "Hematological Effects" and "Preexisting Asthma" in the Precautions section. These two issues are appropriately addressed in the Inclusion/Exclusion criteria for the study; hematological measures are monitored at regularly scheduled intervals or more often if clinically indicated (see below for details). A point-by-point response to the specific issues raised by Public Citizen follows:

1) Gastrointestinal effects – *The letter states that patients are not told of a variety of effects, including perforation of the GI tract, increased risk with longer-term use of the drug, and the asymptomatic nature of some GI problems, which, the letter claims, renders patient monitoring ineffective* (Page 5 of the letter, point 1).

While the consent forms do not mention perforation, a rare complication of ulcer disease, all of the approved consent forms note the possibility of ulcers and bleeding from the GI tract. The consent forms at most of the study sites go even further than the warning in the FDA-approved label, and note the possibility of death from a bleeding ulcer. People are precluded from participating in ADAPT if they have a history of serious ulcer disease or uncomplicated peptic ulcer with symptoms in the 28 days prior to beginning the study. In addition, participants are evaluated regularly by a physician and have their blood checked for signs of anemia that may indicate a bleed. Medical personnel contact participants in between clinic visits to assess problems by phone, and ask participants to come in for further evaluation if indicated. Participants may also call study doctors at any time with any questions or concerns they may have. The occurrence of GI bleeding and other adverse incidents is monitored by the DSMB to detect any effects that may be associated with the treatments being studied.

As Public Citizen asserts, the FDA label for celecoxib states that ulcers and other GI adverse events caused by NSAIDs appear to occur in about 2-4% of patients treated for one year. The label goes on to state that it is unclear how this rate applies to CELEBREX. Regardless, the rate would apply to naproxen, and some of the IRB-approved consent forms note the 1% rate with no time frame specified. The possibility of revising consent forms to optimally reflect risk will be presented by NIA for discussion with the DSMB.

At the October 4, 2002, Steering Committee meeting for ADAPT, committee members agreed that revised consent forms will be submitted to the IRBs, which include the term "perforation" or "hole" in the stomach as possible adverse events associated with the use of naproxen and celecoxib. In addition, the Steering Committee proposed that the rates of GI ulceration quoted from the drugs' labels be replaced with the rates observed during the first 18 months of ADAPT. This rate applies best to the population and doses used in ADAPT. Because of careful screening and monitoring, the number of episodes of GI bleeding has been very low (and none have resulted in perforation or death), lower than that stated in the FDA-approved labels, which refer to a different patient population taking higher doses than those used in ADAPT.

2) Renal and 3) hepatic effects - *The letter cites FDA label information that older people are at greater risk for kidney problems and that information on COX-2 inhibitors' potential for impairing renal function is not being shared. It also notes parts of the label*

which mention risk of death from rare, severe hepatic reactions from the tested drugs. (page 5 & 6 of letter, points 2 and 3)

Again, people are precluded from participating in ADAPT if they have a history of clinically significant liver or kidney disease, or if laboratory parameters fall outside an upper limit that may indicate liver or kidney disease. The possibility of hepatic and renal effects is noted in the consent form, concurrent with the level of risk of these effects and to the satisfaction of six independent IRBs and the DSMB. Liver and kidney function are monitored by laboratory tests of each participant regularly.

4) Hematological effects – *While the FDA-approved label for celecoxib mentions anemia, according to the letter, the consent information does not.* (Page 6 of the letter, point 4)

The hematological effect noted on the label is anemia (low blood count). The label goes on to note that: "In controlled clinical trials the incidence of anemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their hemoglobin and hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss."

The hemoglobin and hematocrit of people who participate in ADAPT are checked one month after beginning the study and every 6 months thereafter. In addition, the consent form includes the phone number of doctors who run the study at each site, should any concerns arise for a participant at any time during the study. The development of anemia in a person taking a drug like those used in ADAPT would most likely be associated with gastrointestinal bleeding, which is clearly covered in the consent form.

It is reassuring that no cases of anemia have been reported as adverse events during the 18 month course of ADAPT to date.

To further clarify this issue, members of the Steering Committee for ADAPT at their October 4, 2002 meeting agreed to add the term "anemia" or "low blood count" as a possible outcome of GI bleeding to the consent form.

5) Fluid retention, edema, and blood pressure – *The letter states that FDA-approved labels suggest a need for caution in patients with high blood pressure, fluid retention, or heart failure, the ADAPT materials only note risk of fluid retention.* (Page 6 of letter, point 5)

Fluid retention, edema, and blood pressure are noted in the consent form concurrent with the level of risk of these effects and to the satisfaction of six different IRBs and the DSMB. In the Precautions section of celecoxib's label, the FDA simply states: "Fluid retention and edema have been observed in some patients taking CELEBREX. Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, or heart failure."

People are precluded from participating in ADAPT if they have a history of clinically significant high blood pressure or any condition that, in the opinion of the study physician, makes it medically inappropriate or risky for a person to enroll in the trial. Elevated blood pressure is noted in neither the Warnings nor the Precautions sections of the FDA-approved labels for celecoxib or naproxen, although it is noted in a listing of adverse events that occurred infrequently in clinical trials of celecoxib. Blood pressure is checked each time participants come in for regularly scheduled clinic visits and more often if indicated.

6) Pre-existing asthma -- *The letter states that FDA's label warns of potentially fatal aspirin-sensitive asthma in susceptible individuals and says such effects are not noted in consent materials.* (Page 6 of letter, point 6)

"Preexisting asthma" is not listed in the consent form because potentially susceptible participants for ADAPT are screened for asthma by physicians, prior to their acceptance into the study. The particular concern, as delineated in the label, is aspirin-sensitive asthma. While it is possible that older people (people enrolled in ADAPT must be at least 70) may not have been exposed to aspirin or other NSAIDs during their lifetimes and so be unaware of their sensitivity to these drugs, it is not probable. Indeed, no case of asthma has been reported during the 18-month duration of the study.

7) Thrombotic tendency, 8) delay in bone healing, and 9) delay in ligament healing -- *The letter points to reports in the scientific literature suggesting that COX-2 inhibitors could increase incidence of myocardial infarction. Further, the informed consent documents do not mention studies suggesting that COX-2 inhibitorscould prevent bone fracture and ligament healing.* (Page 6 & 7 of letter, points 7, 8, and 9)

Public Citizen incorrectly asserts that "thrombotic tendency," "delay in bone healing," and "delay in ligament healing," are included in the Warnings and Precautions sections of the FDA-label. In fact, these items are not mentioned in the FDA label at all. For each of the latter two, Public Citizen cites one reference from the scientific literature. One describes healing problems under experimental conditions in the femurs of rats and genetically altered mice (1 of informed consent references below); the other describes problems 14 days after injury to the medial collateral ligaments of male rats. (2) No data from humans are cited nor do any exist. In fact, upon further reading, the reference by Elder et al., notes: "Therefore, we are unsure whether celecoxib has any influence on the long-term outcome of ligament healing." (2)

Regarding "thrombotic tendency," Public Citizen cites three references, all of which raise concern about an increased propensity towards blood clotting with celecoxib, of concern because this may predispose to adverse events such as heart attacks and strokes. None of the published papers that questions this contention (3, 4, 5) is cited, and certain statements in the cited references that question this are not included, for example, "The CLASS trial with celecoxib demonstrated no significant difference in cardiovascular events as compared with the NSAIDs (ibuprofen and diclofenec)"(6). (In the CLASS trial, as in ADAPT, participants were allowed to continue low dose aspirin.) In two of the references cited by Public Citizen, author Mukherjee states that, "Definitive evidence of such an adverse effect will require a prospective randomized clinical trial." (6, 8)

Finally, Public Citizen fails to mention that an FDA advisory panel convened after celecoxib was approved did not find "any clinically or statistically significant trend with celecoxib to suggest additional cardiovascular risks over comparator drugs" (diclofenac and ibuprofen). (7) Interestingly, like aspirin, evidence indicates that naproxen decreases the risk of cardiovascular events. (3, 6, 8, 9, 10, 11, 12)

In an effort to be fully sensitive to the requirement for full informed consent, ADAPT in fact responded several months ago to reports of a possible increase in cardiovascular events associated with celecoxib, notwithstanding the uncertainties

described above in interpretation of these reports. The consent form for the ADAPT study has been amended at all study sites to reflect the controversy on this possible additional risk. The Steering Committee for ADAPT voted on this action early this year.

References for informed consent

(1) Simon AM, Manigrasso MB, O'Connor JP: Cyclooxygenase-2 function is essential for bone fracture healing. *Journal of Bone and Mineral Research* 17:963-976, 2002.

(2) Elder CL, Dahners LE, Weinhold PS: A cyclooxygenase-2 inhibitor impairs ligament healing in the rat. *The American Journal of Sports Medicine* 29:801-805, 2001.

(3) Silverstein FE, Faich G, Goldstein JL, et al.: Gastrointestinal toxicity with celecoxib vs nonsteriodal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: A randomized controlled trial. Celecoxib Long-Term Arthritis Safety Study. *JAMA* 284:1247-55, 2000.

(4) Wooltorton E: What's all the fuss? Safety concerns about COX-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex). *Canadian Medical Association Journal* 166: 1692-3, 2002.

(5) Cleland LG, James MJ, Stamp LK, Penglis PS: COX-2 inhibition and thrombotic tendency: A need for surveillance. *Med J of Australia* 175:214-217, 2001.

(6) Mukherjee D: Selective Cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. *Biochemical Pharmacology* 63:817-821, 2002.

(7) Throckmorton DC: Comparitive safety of celecoxib, diclofenec and ibuprofen; FDA, 2001: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b 1_07.pdf

(8) Mukherjee D, Nissen SE, Topol EJ: Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 286:954-959, 2001.

(9) Watson DJ, Rhodes T, Cai B, Guess HA: Lower risk of thromboembolic events with naproxen among patients with rheumatoid arthritis. *Arch Internal Med* 162:1105-10, 2002.

(10) Rahme E, Pilote L, LeLorier: Association between naproxen use and protection against acute myocardial infarction. *Arch Internal Med* 162:1111-15, 2002.

(11) Solomon DH, Glynn RJ, Levin R, Avorn J: Non-steroidal anti-inflammatory drug use and acute myocardial infarction. *Arch Internal Med* 162:1099-104.

(12) Bombardier C, Laine L, Reicin A, et al.: Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 343:1520-28, 2000.

Conclusions

In its letter, Public Citizen states: "Thus, there may be additional adverse events about which we are currently ignorant." This is true for any drug. These drugs have been marketed for years and used by millions of people world-wide; still the reality is that they are regularly used for much longer time periods than the at-most 6-month studies evaluated by the FDA for their approval.

Additional information about the potential risks and benefits of these drugs will be most effectively and ethically obtained by testing drugs in informed people under the controlled conditions and medical monitoring of a clinical trial. In addition to contributing to the understanding and possibly treatment of AD, the ADAPT study will carefully monitor subjects to ensure their safety and will generate data on the effects of the long-term use of celecoxib and naproxen in older people.

As Public Citizen concludes, "AD presents a frightening prospect . . ." It is even more frightening, as well as frustrating, because so little can be done, to watch a parent or sibling lose memory and eventually identity, moving inexorably toward death from this disease. Those at risk face the frightening prospect of AD for themselves, and many want to do something. Long-term, controlled clinical trials like the ADAPT study are the best way, indeed, the *only* way, to evaluate potential drugs that may prevent, delay, or slow the progression of AD.

"We do not yet know whether either drug will be able to prevent Alzheimer's disease," says the consent form for ADAPT. People with AD in their families make an informed choice of whether the risks associated with these drugs are balanced against their risk of AD and the benefit of learning more about AD. They know they personally may not benefit from participating in the trial. But the benefit of increasing knowledge about AD is something else that they can pass on to their children.

Revised: 10/7/02