

Question 7: Trials for CV Effects of Non-Selective NSAIDs

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights.....	1
Discussion Text: Question 7	2
Slide with Text of Question 7	5

Highlights

- **NEW STUDIES NEEDED:** All participants agreed that additional cardiovascular safety studies of non-selective NSAIDs are required.
- **INCLUDE NSAIDS IN ALLHAT-TYPE TRIAL:** Dr. Fleming said that ibuprofen and diclofenac should be included in the Temple ALLHAT-type trial if possible.
- **PRACTICE-LEVEL RANDOMIZATION IN LARGE SIMPLE TRIAL:** Dr. Platt suggested a variation of the ‘large simple trial’ in which randomization to a particular drug would be on a practice-level rather than a patient-level basis to provide large-scale randomized studies of drugs “as they are used in regular practice”.
- **TRACKING DEATHS IN OBSERVATIONAL STUDIES:** Dr. Wood asked about tracking deaths in the Medi-Cal database.. Dr. Graham did not respond directly but said that California Medicaid, Kaiser Permanente, Tennessee Medicaid, and several Canadian databases all have linkage to death certificate data.
- **TOUGH WARNINGS GIVE INCENTIVE TO SPONSORS:** Dr. Nissen said that the best way to get the randomized safety trials of non-selective NSAIDs it to provide the incentive of losing the “cardiovascular warning” if the results are good – which argues for “tough” warnings to provide more incentive. Dr. Wood said that this could be an opportunity to differentiate their drug from the competition because of a better safety profile.
- **ANY NEW OTC APPROVALS NEED GOOD SAFETY DATA:** Dr. Wood said that no new OTC NSAID approvals should be given without “really good safety data”.

Discussion Text: Question 7

DR. FLEMING (comment after Question 6 discussion and before discussion of Question 8 and then 7): If we are jumping to 8, just very quickly, in 10 seconds, I would certainly urge, from a public-health perspective, that if there was any way possible to include ibuprofen and diclofenac in the Temple trial, that would be an extremely important added insight.

DR. WOOD: In the Temple ALLHAT trial. Okay.

DR. WOOD (continued discussion of Question 7): Dr. Platt was first on deck.

DR. PLATT: It seems to me unlikely that it will be possible to do conventional randomized trials for many of the now generic non-steroidals, particularly the ones for which you are unlikely to put a very strong warning. Therefore, I suggest that you consider a variation of the 'large simple trial'. Specifically, I think that there is an opportunity to something that is essentially new which is to do large-scale cluster randomized trials in the kinds of environments that Dave Graham described as being good ones in which to do observational studies. The basic logic would be that practices or larger groups would be randomized to prefer ibuprofen as the first drug among a class prefer indomethacin, or for some other others. Those are just examples. That provides good randomization. It provides the opportunity to use the kinds of observational strengths of completely representative populations using the drugs as they are used in regular practice and it is an extremely efficient way to collect the exposure and the outcome

data. It would be efficient and it would provide an opportunity to do--it is essentially a new way to study important questions and I think it would be ideally suited to this kind of question for which I don't think you are going to have another good trial approach.

DR. WOOD: We could take approaches where we actually examine people who were going on therapy in the real world. There are other approaches, as you discussed before. The one caution I would say about using--about just taking away everything that David said is David, himself, acknowledged the Medi-Cal database is not well validated yet and it is has been hard to track deaths in that; right, David? The validity and the mortality.

DR. GRAHAM: Actually, California Medicaid does have linkage to death certificates up through 2002 so, for the older NSAIDs, you could theoretically obtain that data. Kaiser Permanente has linkage to death-certificate data. Tennessee Medicaid, with Wayne Ray, whom you know very well, Alastair, he has linkage to death-certificate data. Then, in Canada, several of the large databases there also have linkage to death-certificate data.

DR. WOOD: I was talking about the Medi-Cal one specifically because of its relevance to this question. That is why. Steve?

DR. NISSEN: On these other agents, probably the key is to create incentives for companies to do this. That means that the way you word the warnings that we suggested will have some impact. I

think that one of the ways you get rid of that warning is to do an adequate trial. This creates an incentive for companies that have popular currently branded agents which are being used a lot to do some more studies, do appropriate studies, so that they can lose that cardiovascular warning. Now, if the warnings are really weak, there won't be any incentive at all to do that. So I think--I am just arguing in favor of your being a little tough on this one because these are drugs taken by tens of millions of people and, if they really do increase by a factor of 1.5 or 1.6, the risk of myocardial infarction and stroke on a population basis, that is a really big deal. So we need clarity here. The only way you get clarity, I think, is with randomized controlled trials. So I think you have got to create an environment that incentivizes people to do those randomized controlled trials.

DR. WOOD: There's one point we've not discussed and I guess, as the Chairman of the NDAC Committee, I think it should come up. It does seem to me that new NSAIDs should not go OTC in the absence of clear safety data. So if somebody's patent expired on that COX-2 right now, I don't think we should let that go OTC without really good safety data that we could evaluate before it went OTC. So that might encourage people to get some of these studies done if they want to switch. Any other comments?

MS. MALONE: I agree with Dr. Nissen. Just to be sure that there is some incentive because, if we make all of these rules more stringent, there has to be some reason for the pharmaceutical companies to continue to develop new drugs. What we want is a win, a double

win, a triple win. We want the patient to win.

DR. WOOD: Right. Although, just to respond to that, Ms. Malone, I agree with that. Actually, in some ways, we are opening up a whole new opportunity for pharmaceutical companies to develop new drugs in that you won't be the fourth COX-2 inhibitor on the market. You may be something that has a safety signal that would be better than someone else. So there actually are huge incentives now to encourage the development of novel compounds that are safer and effective. Yes? Dr. Bathon?

DR. BATHON: In follow up to your comment, I would like to say that one thing that hasn't been said, I think, in three days, is it is nice to know that, if we can keep these drugs on the market, that we will be able to continue to explore the importance of COX-2 in other pathological processes because there may, as yet, be undiscovered applications for these drugs. We are in an era of really targeted treatment to have these kinds of specific inhibitors still available to continue to study new applications is important as well.

DR. WOOD: Of course, people can study--would study--new applications under an IND and they wouldn't need to be available to do that. I mean, all the ones that we saw in the second day were not currently available.

DR. BATHON: Yes, but if you take a drug like thalidomide or something, if you remove it from the market, you give it a pretty bad press and then people aren't too crazy about being in clinical trials.

DR. WOOD: It is back on the market. Any other comments? Then I think-- have we anything else that we need to discuss pressingly? If not, and the most important piece of information I need to give you is one that Kimberly has which is--where is it? The travel agency that you can change your flights to has changed, apparently. That has vanished. So that means you are out of luck. I think we are through. Thanks very much for everybody who stayed to the end and it has been a tough three days. Thank you very much.

Slide with Text of Question 7

7. What additional clinical trials or observational studies, if any, do you recommend as essential to further evaluate the potential cardiovascular risk of the non-selective NSAIDs? Please be specific with regard to which non-selective NSAIDs (i.e., all or only selected agents), trial design, patient populations, control groups, endpoints, duration, sample size, study drug etc.