-----Original Message-----
From: Seligman, Paul
Sent: Thursday, August 12, 2004 11:21 AM
To: Graham, David J
Subject: FW: cox-2 ispe poster- more comments

FYI.

Paul
-----Original Message-----
From: Trontell, Anne E
Sent: Thursday, August 12, 2004 10:31 AM
To: Seligman, Paul
Cc: Trontell, Anne E
Subject: RE: cox-2 ispe poster- more comments

How can David draw a conclusion about one or two strata with 18 cases when he's controlled for >30 variables in his model? The CVRS may not fully adjust with all the empty cells for channeling of COX2s to sicker, older, and higher risk individuals. What are the results of Parivash's study in UHG in this regard? In light of the WHI initiative, we know hat multiple adjustments may not fully control for channeling of certain high or low risk people to different drug products. Particularly since Kaiser uses these products in such a limited fashion, could it be that Kaiser pts on high dose rofecoxib are intolerant of other NSAIDs, or have special needs to warrant the higher dose?

I also do not understand why a nonsignificant finding for >25 mg rofecoxib is singled out when there are other point estimates >1 that are statistically significant. Eg naproxen and NSAIDs.

If the conclusions stand (and I would defer to someone on site who can get more data and spend time talking with David, like Bob O'Neill, to comment on the methods) then I think the recommendation about high dose rofecoxib is unnecessary and particularly problematic since FDA funded this study and David's travel to France to present it. If FDA disagrees with David's conclusions and/or recommendations, David might be asked as a condition of this being cleared to display an additional panel with alternative FDA opinion on this. Pulling that together will be hard to do at this late date. Another option would be to use one of our DSaRM members like Strom or Furberg to review the study methodology and findings. Again time is short for this.

In fact, in light of the quick turnaround review requested on this project, I think a preferred option for a significant conclusion and recommendation such as David appears to want to make is for him to defer this poster presentation entirely from ISPE and instead write and submit a complete article to a peer-reviewed journal. That would give other scientists within the Agency and also in the scientific community, a fair opportunity to comment on a more extensive discussion of its ethods and to review the strength and merits of its conclusions. Given vacations and the short time before ISPE, I cannot fully comment on the merits of this study and suspect you are in a similar situation.

The reason to be so careful is that health plans and PBMs will likely act on the conclusions and recommendations alone, particularly if there

if the lead author is an FDA employee.

However this study is presented, the mfg (Merck?) needs to know before it becomes public so they can be prepared for extensive media attention that this will likely provoke.

Feel free to share all or part of this email with David if you think my points have merit at this time.

Anne