

Annals of Internal Medicine

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April 25, 2003

Gregory P. Geba, MD
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REF: Typescript M03-0472

Dear Doctor Geba:

Thank you for submitting to *Annals of Internal Medicine* your manuscript, "The Gastrointestinal Tolerability and Effectiveness of Rofecoxib versus Naproxen in the Treatment of Osteoarthritis: 'ADVANTAGE.'" One of our associate editors and I read the paper. It was also read by one of our statisticians and was discussed at a weekly meeting of the editorial staff.

We are interested in publishing your paper as an **Article**. Of course, we cannot give you assurance of final acceptance at this point. Before we can consider it further, however, you must prepare a revision that deals satisfactorily with the concerns and suggestions enclosed with this letter.

1. Congratulations on conducting an important trial. We believe that our readers will find it interesting and that its results provide important information about the frequency of adverse events from rofecoxib and naproxen. We do have several suggestions aimed at improving presentation and analysis.
2. In general, follow CONSORT guidelines (Ann Intern Med 2001;134:657-694) for reporting trials. Add a figure (example is on page 666) that maps the flow of the participants through each stage of the trial.
3. Abstract: Polish sentences that describe trial participants. Under measurements, specify whether global assessment of disease was self-reported. Do not capitalize weeks. Add the word "statistically" before sentences that describe "significant" and "no significant differences." Polish language regarding subgroup results; avoid jargon such as "aspirin user cohort." Clarify the last sentence of the conclusion; be specific about risk factors and avoid using the term "cohort."
4. Please work on the content and presentation of the Introduction. As is, the first two paragraphs don't set up a compelling rationale for the

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current trial. Avoid passive voice in the Introduction, and avoid jargon such as "pure OA study." Finally, be more concise regarding study aims.

5. Give the reader more detail regarding how patients were recruited. (See Ann Intern Med 2002;137:10-16 for suggestions on types of information relevant to recruitment that should be added.)
6. Delete the sentence "Exclusion criteria were minimal to maximize the external validity of the trial" (p. 7). Clarify whether disease and health status outcomes (PGDAS, SF 36, AUSCAN Hand Index) were interviewer-administered (p. 8).
7. State whether randomization was stratified by center (p. 8). State methods that were used to ensure allocation concealment (e.g., identical blister packets of drugs distributed by pharmacies??).
8. Provide more specific details regarding how adverse events were assessed (p. 8). Was an open-ended questionnaire used? Were patients prompted regarding specific types of adverse events? Were patients queried about the frequency and/or severity of adverse event symptoms? Who queried patients about adverse events?
9. Clarify whether patients were told that they could/should use medications for gastrointestinal symptoms. If so, when were they told this, and were any specific medications recommended? Also, clarify whether patients were told that they should discontinue trial medications and/or aspirin if they experienced particular symptoms.
10. Add a statement that gives the funding source and that defines the role of the funding source in data collection, analysis and interpretation and in the decision to submit the manuscript for publication. Place this statement after the Statistical Analysis section and before the Results section (p. 11).
11. Describe follow-up and numbers of drop-outs by group.
12. Please pay close attention to the enclosed comments from the statistician regarding analyses. You must specify amounts of missing data by group at both the 6-week and the 12-week time-points for primary outcomes and efficacy outcomes and discuss implications of any important missing follow-up data.

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13. Shorten the Results section. Avoid redundant information in tables, figures, and text. Clarify what is meant by "The later defined the subgroup of previously GI intolerant patients" (p. 11). Use the word "statistically" when describing "significant" differences (p. 12). Avoid wordiness and jargon. For example, delete the phrase, "For the prespecified secondary safety endpoint" (p. 12). Do keep the text information about cardiovascular events (p. 12), and do not add a separate table that gives these events.
14. Use fewer than 6 total tables/figures to present results. Delete Table 2; incorporate some of this important baseline information into Table 1. Consider whether information in Figures 1 and 3 could be presented in one figure, and likewise, whether information in Figures 4 and 5 could be presented in one figure. If not, consider deleting the efficacy analysis figures (4 and 5), and presenting efficacy information only in the text.
15. Add a section that describes study limitations to the discussion. Be more circumspect, balanced, and specific regarding numbers of hospitalizations and deaths and costs that can be attributed to NSAIDs (p. 16). Use of COX-2 inhibitors will not obviate all hospitalizations and deaths, and unselective use of COX-2 inhibitors could increase costs significantly.
16. Edit the revised manuscript closely. Change passive to active voice whenever possible and get rid of unnecessary words, long phrases and redundant sentences. Avoid confusing statistically significant differences with clinically significant differences. Rather straightforwardly emphasize the size of the differences (which our senior editor and many associate editors interpreted as small) and the preciseness of these estimates. Avoid presenting and discussing implications in a slanted, overly positive manner. Moreover, several associate and senior editors thought that the presentation still merits significant improvement.
17. Since we suggest a fairly large number of clarifications and changes, we may have additional comments/suggestions for the revised version.

Requests for technical revision are outlined on a separate sheet (enclosed) prepared by one of our production editors.

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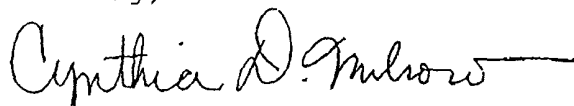
Each author must approve the revised version of the manuscript and personally sign the enclosed Authors' Form. You must complete and sign a Conflict of Interest Notification Page and each author must also complete a Conflict of Interest Disclosure Statement.

Please send your revised manuscript to us within the next 4 weeks. If you are unable to meet this deadline, let us know immediately. When you return the revised version, send 3 copies of the manuscript and figures, and 3 copies of a letter outlining how you have responded to each comment. Your response should be grouped under the headings: Editor, Statistician, and Technical Revisions, as appropriate. Each group of responses should be numbered to correspond with those on the comments. Please restate each comment and follow it with your response. Refer to a given page, paragraph, and line; say briefly what you did, why you did it, and where in the revised version the changes can be found (page, paragraph, and line).

We ask that you also submit an electronic (diskette) version of the manuscript you return to us in response to this letter along with the paper version. For your convenience, we have included a copy of the *Annals* Manuscript/Disk Preparation and Word Processing Instructions. We appreciate your cooperation.

We look forward to receiving your revised manuscript.

Sincerely,



Cynthia D. Mulrow, MD, MSc, FACP

CDM/rb

Statistical Review of Lisse et al. (M03-0472)

"The Gastrointestinal Tolerability and Effectiveness of Rofecoxib Versus Naproxen in the Treatment of Osteoarthritis: "ADVANTAGE." A Randomized Controlled Trial.

Generally, the methods used and the reporting of results was appropriate. I thought the authors did a nice job of analyzing the data. I only have a few points to make:

1. In figures 1 et al., there are pvalues comparing naproxen to rofecoxib at each of week 6, week 12, and end of study. This is not quite appropriate. It is sort of like doing interim analyses at weeks 6 and weeks 12 before doing the 'final' analysis at end of study. The reason for this is that the patients who fail by week 6 are not only included in the analysis at week 6, but also at weeks 12 and end of study. I understand that the authors have reason to want to illustrate this in this nice figure, but the presentation of the three pvalues is not really appropriate. The better way to describe this is as the authors do later in their survival curves, by showing hazard ratios, statistical significance, etc.
2. In general, the figures aren't consistent in reporting pvalues: I see that only significant pvalues are reported and that when pvalues are not significant there is a little footnote saying "NS" (eg figures 2a and 2b). Not only should the placement be consistent, but putting "NS" is generally not helpful—NS includes the range of results where $p = 0.06$ to $p = 1.00$. So, please include all pvalues instead of stating "NS."
3. The point raised about the pvalues in figures (in point 2. above) is also seen in the text. It is stated that things are 'similar' but no rationale is given for similarity whereas when differences are seen, the authors consistently state a pvalue. Is the 'similarity' referred to due to insignificant pvalue or to small observed difference of estimates, or both? Note that it is quite possible (given the rare nature of some of the AEs) to see large differences (eg a 1% versus a 5% incidence) that do not reach statistical significance.
4. In Figure 3, it is stated that "treatment groups separated by week three, were significant at week 6..." Please be more clear about "were significant at week 6." This should be based on the survival analysis, not on the fisher's exact tests shown in figure 1.

***Annals of Internal Medicine* Revision Requirements**

Manuscript #:	M03-0472
First Author:	Lisse

Please Include with Revision:

- Authors' forms with original signatures. Please note that we cannot accept faxed copies or photocopies.
- Signed conflict of interest forms, enclosed.

Text

- Please do not use (write out) the following abbreviations: OA, AE, qd, bid, PUB, CV, BP. Please define ADVANTAGE, AUSCAN OA Hand Index LK3.OS, and VIGOR at first mention.
- Please list the members of the ADVANTAGE study group in an appendix rather than in the acknowledgments. Also, please provide first names for all members if possible.

References

- Reference citations in the text should be typed on line, in full type size, within punctuation, and in parentheses, for example, (1). Do not use superscript, and do not electronically link references with reference citations.
- For references 2 and 3, please list all editors when six or fewer; when seven or more, list the first six and add "et al."

Tables and Figures

- There are too many figures and tables for this manuscript. Please reduce to no more than 6 figures or tables, including the figure that the Editor has asked you to add. Please see the Editor's letter for more specific instructions.

Permissions

- Provide letters of permission from everyone listed in the acknowledgment section.

Electronic Manuscript Submission

- Please submit a separate electronic file for the manuscript, tables (one file for all tables), and figures (individual file for each figure). We strongly prefer PC-formatted diskettes rather than Macintosh-formatted diskettes.