



JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
415 N. Washington Street, 2nd Floor
Baltimore, Maryland 21231

10 July 2019

Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Counting 102

I wrote previously on counting (Counting 101; 25 June 2019). This memo is more on counting.

Investigators in VIGOR (Vioxx Gastrointestinal Outcomes Research) published results in the NEJM, 23 Nov 2000 (*Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*) in which they concluded

In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor.

Five years later the publication generated an “expression of concern” by NEJM editors (8 Dec 2005), a rebuttal of the concern by study investigators (16 Mar 2006), and an “expression of concern reaffirmed” by NEJM editors (16 Mar 2006).

The concerns were due, in part, to the fact that three cardiovascular events were not included in the database for publication because they occurred after the cutoff date for inclusion and because at least two of the authors knew of the events before the paper was submitted for publication. The NEJM editors wrote

This date (the cutoff date for CV events), which the sponsor selected shortly before the trial ended, was one month earlier than the cutoff date for the reporting of adverse gastrointestinal events. This untenable feature of trial design, which inevitably skewed the results, was not disclosed to the editors or the academic authors of the study.

My sisters and brother, counting cars on trains on the way home from school, had no trouble knowing when to start and stop counting, but the situation is different in trials. Data flow continues after the trial stops. As a result, counts have to be made from frozen datasets using an arbitrary cutoff date.

Rules of thumb for cutoff dates for data freezes are:

- 1 Chose independent of data trends,
- 2 Chose with discussion and consent of investigators (rule violated in VIGOR by allowing funder to specify cutoff date for CV events),
- 3 Chose date to apply across the board to all counts (rule violated in VIGOR by having an earlier cutoff date for CV events than for gastrointestinal events),
- 4 Chose by study investigators independent of sponsor (rule violated in VIGOR by allowing sponsor to specify cutoff date for CV events),
- 5 Chose to be sufficiently in the future to allow data to clear pipelines, to be edited and cleaned, and for investigators to complete essential activities including event adjudication, if applicable, and to track persons lost to followup for mortality or occurrence of serious adverse health events,

- 6 Make a written record of counting rules in creating frozen dataset (important because questions, as seen in VIGOR, can come long after publication and investigators may need the written record to verify analyses done years earlier),
 - 7 State the freeze date and rationale for date; report “as of date” (cutoff date for freeze) in tables and figures containing counts,
 - 8 If, for whatever reason, it becomes necessary to “thaw” and freeze again, all counts should be checked and updated as necessary before submission,
- and
- 9 If counts change because of information coming to light after publication, journal editors should be informed and authors should proceed as instructed in communicating the change to readers of the journal.

The freeze date is important because it is in the critical path to paper writing. There is no paper writing until datasets have been merged and frozen. Discussions regarding choice of date will have elements of tugs-of-war between those who want to freeze sooner rather than later so they can get on with paper writing and those (usually people who have to do the merging and freezing) who want it later to reduce the risk of “thaws” after freezing.