(Sunday) 28 November 2010

Memorandum

To: Curt Meinert

Fr: CLM

Re: Systematic reviews and meta-analyses

It has been sometime since my last letter – been busy doing other things.

On previous occasions I have written giving you the "benefit" of observations made while looking over your shoulder. This time I am writing for answers to questions I have.

Why do people assume trialists don't do any analyses or reviews before undertaking trials?

Go to any meeting, such as the journal club a week or so back, and you will hear "Do a meta-analysis before considering a trial". It drives me crazy.

First, because it is annoyingly "preachy" and self-righteous.

Second, because it is born of a presumption not supported by facts. The presumption is that trials are done on a whim without any review or analysis. I know you know that sponsors and funding agencies do not hand out money on "whims".

Third, because the admonition is not connected to reality. If the trial is a phase I or II trial there is basically nothing to meta-analyze and if it is a phase III or IV trial usually the only option the trialist has is to respond to the RFA or RFP for the trial or to pass.

That leaves only the few phase III/IV trials that are investigator-initiated where the trialist is in control. I don't need to remind you that those trials don't get funded unless you can convince review groups that they are necessary.

So, to whom are the meta-analysts preaching?

A second question is why do you think meta-analysts and systematic reviewers have such faith in their new found tool when they have such doubts about the validity of individual trials? Sit through any journal club review of a trial and the overriding issues will be bias and "generalizability". But give the same people disparate data from different trials and voila! After some combining and grinding they come up with a global conclusion that is truth! Explain please.

With all the people telling trialists how to do trials and mandates for registration, data sharing, and valid analyses, how about a few mandates for meta-analysts and systematic reviewers?

I know you have said if ever you got to be president (not worried) you would require would-be meta-analysts and systematic reviewers to:

1. Take a course in "asking etiquette",
2. Have done at least one trial,
3. Have prepared at least one de-identified dataset, and
4. Have supplied data for at least one meta-analysis or systematic review,

before allowing the person to ask for someone else's data.

I was around when you received the e-mail below a couple of weeks back. My ears are still ringing!

> Dear Dr. Meinert:
>
> Your publication, "Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results" has met the initial criteria for inclusion in our meta-analysis.
>
> Our lab is completing a Cochrane Systematic Review entitled "Cox-2 Inhibitors for the Prevention of Melanoma". We are interested in finding out more information about your trial so that we may assess it for final inclusion.
>
> Could you kindly answer the questions below?
>
> Please provide data in de-identified format. Thank you in advance:
>
> Was melanoma incidence measured?
>
> If melanoma incidence was measured, during which part of the trial was it measured?
>
> If you recorded melanoma outcomes, please also answer the following:
>
> How many patients were diagnosed in each arm of the trial after they received treatment?
>
> Were all patients analyzed in their original groups (intention to treat analysis)?
>
> Who was blinded during the trial?
>
> The information can be emailed directly to me, at your earliest convenience.

From your mutterings I know you saw the request as a half-baked fishing trip to see what might be dragged in. Why a paper on design and methods of an Alzheimer's disease prevention trial meets "initial criteria for inclusion" is beyond me.

The e-mail is written as if you should be pleased that your trial is under consideration for inclusion. So why weren't you?

I know why. Because sharing data is a PITA! I know that from your experience in supplying ADAPT de-identified data to the Oxford systematic review mill. It involves a lot of work and endless questions from people who do not bother reading the documentation you provided.

The Cross Trial Safety Analysis of celecoxib, involving harvest of data from six trials (ADAPT being one), took three years to do. The Oxford meta-analysis of celecoxib trials is in its 4th year with the end still at least a year away.

The notion of formal meta-analyses serving as prerequisites to doing trials brings to mind that sign over your mechanic's bench in Sleepy Eye "When you are up to your ass in alligators, it's hard to remember you started out to drain the swamp".

Alas, you live now in a world where the higher calling is harvesting data from others than producing your own. It is as if we have forgotten that we have to have poor souls doing trials, if only to keep the meta-analysts and systematic reviewers employed.

If Samuel Johnson had ended up being a trialist instead of a lexicographer he may well have written (slight rewording of his preface to his Dictionary of the English Language, 1755):

> *It is the fate of those who toil at the lower employments of life, to be rather driven by the fear of evil, than attracted by the prospect of good; to be exposed to censure, without hope of praise; to be disgraced by miscarriage, or punished for neglect, where success would have been without applause, and diligence without reward.*
>
> *Among these unhappy mortals is the **doer of trials**; whom mankind have considered, not as the pupil, but the slave of science, ... doomed only to remove rubbish and clear obstructions from the paths of Learning and Genius, who press forward to conquest and glory, without bestowing a smile on the humble drudge that facilitates their progress. Every other author may aspire to praise; the **trialist** can only hope to escape reproach, and even this negative recompense has been yet granted to very few.*

Have a nice day!