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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Show me your data

"The ClinicalTrials.gov results database was launched in September 2008 to implement Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801), which requires the submission of "basic results" for certain clinical trials, generally not later than one year after the Completion Date (see Primary Completion Date data element on ClinicalTrials.gov.) Submission of adverse event information was optional when the results database was released and became required in September 2009. Results information for registered and completed studies is submitted by the study sponsor or principal investigator in a standard, tabular format without discussions or conclusions. The information is considered summary information and does not include patient-level data." (from http://clinicaltrials.gov/ct2/about-site/results)

The primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the prespecified protocol or was terminated.

Applicable clinical trials, as defined in the Food and Drug Administration Amendment Act (FDAAA), are:

- Trials of drugs and biologics: Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to FDA regulation
- Trials of devices: 1) Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and 2) pediatric postmarket surveillance required by FDA

Applicable clinical trials generally include interventional studies (with one or more arms) of FDA-regulated drugs, biological products, or devices that meet one of the following conditions:

- The trial has one or more sites in the United States
- The trial is conducted under an FDA investigational new drug application or investigational device exemption
- The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research

The one year time requirement for deposit is unrealistic, tantamount to requiring investigators to make their data available to others before they have had a chance to analyze and publish their results, and indifferent, if not actually hostile, to publication.

Consider the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT). The decision to suspend treatment took place mid December 2004 because of safety concerns. It took 23 months and five submissions after the decision before results were published:

1st submission: *Journal of the American Medical Association* (JAMA): 13 Oct 2005; rejected 9 Nov 2005
2nd submission: *Archives of Internal Medicine*: 21 Nov 2005; rejected 1 Dec 2005
3rd submission: *Lancet*: 22 Dec 2005; request for revisions 16 Jan 2006; revisions submitted 2 Feb 2006; rejected 20 Mar 2006
4th submission: *British Medical Journal* (BMJ): 30 April 2006; rejected 18 May 2006
5th submission: *Public Library of Science* (PLoS): 25 Jun 2006; request for revisions 25 Jul 2006; revisions submitted 15 Aug 2006; second request for revisions 5 Sep 2006; 2nd revision submitted 11 Sep 2006; accepted 29 Sep 2006 (Martin BK, et. al., Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-inflammatory Prevention Trial; *PLoS Clin Trials* 17 Nov 2006)

For insight into the publication process we identified multicenter randomized trials published in the last half of 2011 in five major journals.

Ann Int Med. 4
BMJ. 8
JAMA. 15
Lancet.. 31
NEJM.. 51
Total. 109

Most of the trials were registered on clinicaltrials.gov (97 of the 109 trials). Almost all of the registrations were updated in 2011 or later (92 out of the 105 with "Last updates" dates listed).

Status as of last update was classified as "active" (still enrolling or treating), "terminated", or "completed".

	Status				
	Active	**Terminated**	**Completed**	**Not stated**	**Total**
Ann Int Med	0	0	4	0	4
BMJ	1	0	6	1	8
JAMA	4	2	8	1	15
Lancet	7	0	22	2	31
NEJM	11	6	33	1	51
Total	**23**	**8**	**73**	**5**	**109**

Registration also indicated sources of support and whether results are posted.

	Source of funding					
	Ann Int	**BMJ**	**JAMA**	**Lancet**	**NEJM**	**Total**
Government	0	7	10	9	20	46
Industry	2	1	3	13	25	44
Private/foundation	2	0	1	8	2	13
Other	0	0	1	1	4	6
Total	**4**	**8**	**15**	**31**	**51**	**109**

	Results posted*	
	Yes	**No**
Ann Int Med	1	3
BMJ	0	6
JAMA	4	6
Lancet	4	17
NEJM	18	20
Total	**27**	**52**

* For trials listed as completed or terminated

Time from completion/termination to publication is shown for the 65 completed/terminated trials with dates listed. The time is the difference between publication (the midpoint of the 6 month publication period – 1 Oct 2011) and completion/termination date to the nearest quarter year. Negative times (three) arise because the completion date listed is after the publication date.

Just a few over one-third were published within a year of completion/termination. The median time from completion/termination to publication was 17 months. The median is likely to be more for publications not appearing in first line journals, given the propensity of authors to start with high profile journals and to move to lower profile journals if rejected by high profile journals.

	Months from completion/termination to publication					
	Ann Int	**BMJ**	**JAMA**	**Lancet**	**NEJM**	**Total**
-12 - -6					1	1
-6 - 0				1	1	2
0 - 6			2	1	8	11
6 - 12			3	3	3	9
12 - 24		1	1	7	9	18
24 - 36	3		2	1	9	15
36 - 48			1		2	3
48 - 60			1		2	3
60 - 120				1	2	3
Total	**3**	**1**	**10**	**14**	**37**	**65**
Median time to publication: 17 months						
?*	1	5	0	8	1	15
Total	**4**	**6**	**10**	**22**	**38**	**80**

* Completion/termination date not stated

The one year time requirement for posting results is at odds with reality. The deadline requires investigators to divert energies and resources to complying with the deadline at the expense of energies devoted to analysis and publication. The priority should go to publication. Deposit should be tied to publication. Ultimately deposit, absent publication, would be required if results are not published.

The advantages of the change would be several.

First, the change would place emphasis where it should be: On publication. The present statement is moot on publication. The requirement for deposit independent of publication is hostile to publication to the extent that it serves to reduce drives to publish. The drive and

means of investigators to publish diminishes with the decay of the study infrastructure following conclusion of a trial. The support for data processing and analysis is time limited. Typically, in government-funded trials, funding ends soon after completion. The more time and energy spent meeting deposit requirements, the less for publication.

Second, the change would be in keeping with the reality of data preparation and analysis following completion or termination of a trial. It can be at least a year before there is a finished analysis dataset. It may take several months after the last person is seen before data harvests are complete and several more thereafter before there is a final count of events. For example, it was about a year after the decision to stop use of tolbutamide in the University Group Diabetes Program (UGDP) before there was a final count of deaths because of efforts after termination to determine vital status for people who dropped out of the study. It was 18 months from the decision to stop the treatment to publication of results.

Trials involving clinical events may require panels to make determinations as to whether persons are counted as having events. If final counts are based on adjudication processes undertaken after the trial is finished, it may take months to implement and complete those processes.

Third, tying deposit to publication avoids troubles investigators can have if counts differ from those published. One need only review the troubles VIGOR investigators had in answering "expressions of concern" by editors of the NEJM because of count discrepancies (NEJM 2000;343:1,520-8; 2005;353:2,813-4; 2006;354:1,193) to be wary of deposits not linked to publication datasets.

To be sure, the counts in what is deposited can be labeled as preliminary, but that qualifier will be forgotten if counting troubles come calling.

In the rush to make data available, we had best be careful to not run those who generate them out of town by robbing them of their birthright to be first to analyze and report. The deposit requirement should be amended to allow for a more realistic time limit and to encourage publication by tying deposit to publication.

Thanks to Jill Meinert and Betty Collison for assistance in identifying the trials and tabulation of information on registrations sites.